# Non viral hepatitis

By

**Ibrahim Negm**

*Professor of Tropical Medicine*
*Al Azhar University*

The liver may be affected either directly or indirectly by many agents of infection other than viruses.

These agents may be:-

- Bacterial.
- Fungal.
- Parasitic infections.
- Ricketsial.
- Spirochetal.
- Protozoal.

# *Bacterial*

Bacterial

# Pyogenic Liver Abscess

## OVERVIEW

1. Pyogenic liver abscess is a life-threatening condition.
2. The incidence varies but is estimated to be 8 to 20 per 100,000 hospital admissions in the United States.
3. Improvements in prognosis have been seen in the 2000s, but delays in diagnosis or failure to recognize this condition can result in high morbidity and mortality rates.
4. This is often associated with other medical conditions.

## MICROBIOLOGY

1. Cultures of blood or abscess contents are positive in most cases.
2. Lesions are often polymicrobial.
3. Klebsiella species (particularly Klebsiella pneumoniae) have overtaken Escherichia coli as the most commonly reported causative bacteria.
4. Microaerophilic organisms, particularly Streptococcus milleri, are increasingly common causes but need careful cultivation to isolate.

5. Anaerobic organisms are commonly isolated from polymicrobial abscesses.
6. Unusual organisms include Salmonella, Haemophilus, and Yersinia spp. Tuberculosis, actinomycosis, and melioidosis also occur, especially in patients with defective immunity (e.g., HIV infection, post-transplantation status).

## EPIDEMIOLOGY

1. Pyogenic liver abscess is rare; population-based studies report 11 cases per million per year.
2. It is more common in middle-aged and older people.
3. Liver abscess often occurs in patients with a predisposing medical condition:
    - Biliary disease
    - Hypertension
    - Malignant disease

- Previous abdominal surgery or endoscopic procedure
- Diabetes mellitus
- Cardiovascular disease
- Crohn’s disease
- Diverticulitis
- History of trauma

4. The gender distribution is equal.
5. No geographic or racial differences are noted.

## PATHOGENESIS

1. Pyogenic infection is carried to the liver through the blood or bile. Frequently, no infective source is found (cryptogenic liver abscess); however, when one can be identified, common sources include the following:
   - Cholangitis, secondary to biliary stricture, stones, or endoscopic intervention.
   - Intra-abdominal sepsis (e.g., diverticulitis, peritonitis).
   - Generalized septicemia.
   - Dental infection.

## Bacterial

- Trauma, including liver biopsy or surgery
- Secondary infection of a preexisting liver cyst, neoplasm (including after ablative therapy), or rarely an amebic abscess

2. The right lobe of the liver is the most frequently involved.
3. Abscesses may be single or multiple; those caused by hematogenous spread are frequently multiple.
4. The abscess contains polymorphonuclear neutrophils and necrotic liver cells surrounded by a fibrous capsule.

Bacterial

# CLINICAL FEATURES

## 1. History

TABLE 28.2 ■ **Presenting symptoms found in a retrospective study of 79 patients with pyogenic liver abscess**

| Symptom | Frequency (%) |
|---|---|
| Fever | 89.6 |
| Right upper quadrant pain | 72.2 |
| Chills | 69.0 |
| Nausea | 43.1 |
| Vomiting | 32.3 |
| Weight loss | 26.1 |
| Jaundice | 21.4 |
| Headache | 17.5 |
| Myalgias | 11.9 |
| Diarrhea | 10.7 |

From Rahimian J, Wilson T, Oram V, Holzman RS. Pyogenic liver abscess: recent trends in etiology and mortality. *Clin Infect Dis* 2004; 39:1654–1659.

2. Physical examination

- Fever
- Finger clubbing (rare)
- Jaundice (in 33%)
- Tender hepatomegaly
- Classic triad of fever, jaundice, and tender hepatomegaly found in less than 10% of patients.

Bacterial

# *DIAGNOSIS*

## 1. Laboratory findings

TABLE 28.3 ■ **Laboratory features in pyogenic liver abscess**

| Feature | Frequency (%) |
|---|---|
| Increased erythrocyte sedimentation rate | 100 |
| Leukocytosis | 75 |
| Anemia | 50 |
| Elevated serum bilirubin level | Common |
| Elevated serum alkaline phosphatase level | Common |
| Increased serum aminotransferase levels | Common |
| Prolonged prothrombin time | Common |
| Decreased serum albumin level | Poor prognostic sign |

2. Diagnostic imaging

a. Chest radiograph abnormal in 50%:
   - Elevation of right hemidiaphragm
   - Blunting of right costophrenic angle
   - Atelectasis
   - If a gas-forming organism is the cause of abscess, fluid levels may be visible below the diaphragm.

b. Ultrasonography
   - Round, oval, or elliptoid lesion
   - Irregular margin
   - Hypoechoic with variable internal echoes

c. CT

- Highly sensitive; detects up to 94% of lesions
- Lesions show reduced attenuation and possibly enhance with contrast

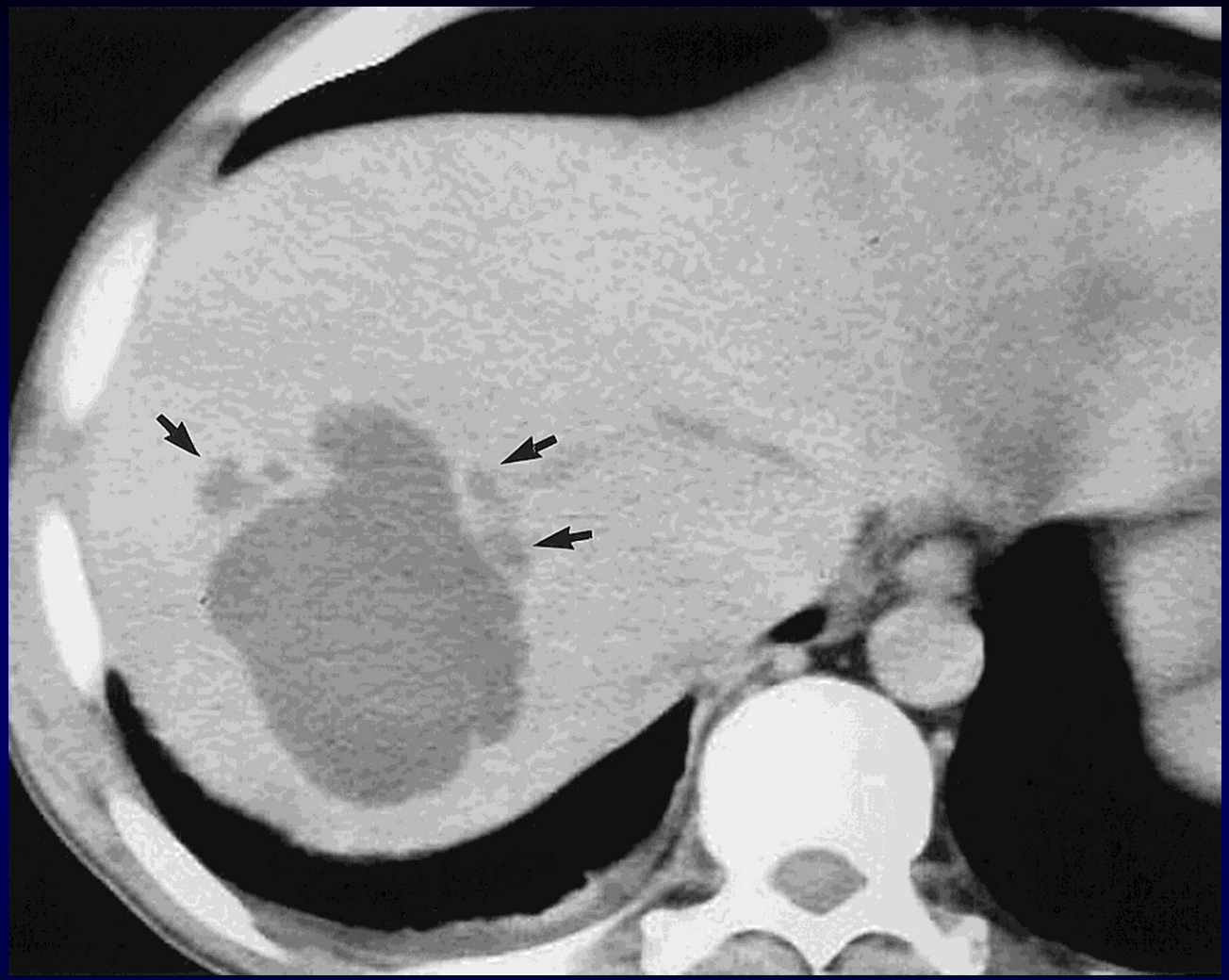
d. MRI

- More sensitive at detecting small lesions than CT
- Lesions have low signal intensity on T1-weighted images and very high signal intensity on T2-images; lesions enhance with gadolinium

e. Radioisotope study

- Gallium is avidly taken up by abscesses

# Pyogenic abscess.



Pyogenic abscess. Delayed-phase contrast-enhanced CT scan shows a large, hypoattenuating lesion in the right hepatic lobe with thin peripheral enhancement and surrounded by other smaller hypoattenuating areas (arrows). These smaller abscesses cluster or aggregate in a pattern that suggests coalescence into a single large cavity.

3. Microbiology

- Blood cultures should be taken before initiation of antibiotic therapy.
- Positive blood cultures occur in 50% to 100%.
- Aspiration of the abscess increases the yield of a positive microbiologic diagnosis.
- In polymicrobial abscesses, all the causative organisms may not be present in the blood.

# COMPLICATIONS

- Septicemia
- Metastatic abscess
- Septic shock
- Acute respiratory distress syndrome
- Renal failure
- Rupture

# Treatment

- In the past, standard treatment involved open surgical drainage of the abscess in combination with broad-spectrum antibiotics.
- Studies since the 1990s have shown improved results with either percutaneous drainage or aspiration in combination with antibiotics.
- Some patients can be managed medically without surgery or aspiration.
- It is usually possible to combine diagnostic and therapeutic aspiration in these patients.

## Bacterial

- Complications of drainage include hemorrhage, perforation of a viscus, infection from the drain, and catheter displacement.
- Antibiotic therapy should include coverage against gram-negative organisms as well as microaerophilic and anaerobic organisms.
- Empiric first-line regimens are as follows:
  - Suspected biliary source: ampicillin + gentamicin + metronidazole
  - Suspected colonic source: third-generation cephalosporin + metronidazole

## Bacterial

- Antibiotic therapy is usually intravenous initially.
- The duration of intravenous antibiotic therapy and the decision to change to oral therapy are governed by the individual clinical response.
- Antibiotic use for a total duration of 2 to 3 weeks is recommended.
- Surgical intervention may be required if the patient fails to respond rapidly to therapy; a flexible approach must be adopted.

# Prognosis

- Untreated pyogenic liver abscess has a mortality rate approaching 100%.
- Case series in the 2000s have reported mortality rates as low as 2.5% but usually 10% to 30%, depending on the underlying cause of the abscess and associated medical conditions.
- Improved mortality rates are thought to result from advanced imaging and diagnostic techniques and the use of percutaneous drainage.

# Other Bacterial Infections Involving the Liver

Bacterial infections can affect the liver directly and often give a clinical picture of acute hepatitis.

# LEGIONELLA PNEUMOPHILA

- Pneumonia is the predominant clinical manifestation; abnormal liver biochemical test levels are frequent, usually without jaundice and without affecting the clinical outcome.
- Liver histologic features are nonspecific, with portal infiltration, microvesicular steatosis, and focal necrosis; occasional organisms are seen.
- Initial treatment is with a fluoroquinolone or macrolide antibiotic.

# STAPHYLOCOCCUS AUREUS (TOXIC SHOCK SYNDROME)

- This multisystem disease is caused by the staphylococcal toxic shock syndrome toxin (TSST-1) and has a mortality rate of 8%.
- Originally described in association with tampon use, it is now more frequently a complication of Staphylococcus aureus infections in surgical wounds, mostly in women.
- Typical findings include fever, a scarlatiniform rash, mucosal hyperemia, vomiting, diarrhea, and hypotension, with rapid development of multiorgan failure.

## Bacterial

- Hepatic involvement is almost always present, results from hypoperfusion and circulating toxins, and is marked by deep jaundice and high serum aminotransferase levels.
- Liver histologic findings include microvesicular steatosis, necrosis, and centrilobular cholestasis.
- The diagnosis is confirmed by culture of toxigenic S. aureus from vaginal swabs, blood, or other body sites or by demonstration of TSST-1.

# Treatment

- Intravenous clindamycin plus nafcillin for methicillin-sensitive isolates or
- Vancomycin or Linezolid for methicillin-resistant isolates;
- Intravenous immune globulin may be beneficial for cases of toxic shock syndrome caused by Streptococcus pyogenes.

# CLOSTRIDIUM PERFRINGENS

- This is usually a mixed anaerobic infection that results in rapid development of local wound pain, abdominal pain, and diarrhea; it is associated with myonecrosis or gas gangrene.
- Jaundice may develop in up to 20% of patients with gas gangrene and is predominantly a consequence of massive intravascular hemolysis caused by the bacterial exotoxin, with resulting unconjugated hyperbilirubinemia.

## Bacterial

- Liver involvement may include abscess formation and gas in the portal vein.
- Hepatic involvement does not appear to worsen mortality rates, which average 60%.
- Treatment is with intravenous penicillin and clindamycin.

# LISTERIA MONOCYTOGENES

- This is characterized by meningoencephalitis and pneumonitis; hepatic involvement in adult human infection is rare.
- Neonates and patients with underlying chronic liver disease or immune deficiency are most commonly affected.
- Serum aminotransferase levels are typically very high.

## Bacterial

- Patients may present with a single abscess, multiple microabscesses, or diffuse or granulomatous hepatitis; the outcome is worse with multiple abscesses.
- Treatment consists of abscess drainage and the combination of (amino) penicillins and aminoglycosides, typically for 3 to 4 weeks.

# NEISSERIA GONORRHOEAE

- Half of all patients with disseminated gonococcal infection have abnormal liver biochemical test levels, mainly elevated serum alkaline phosphatase levels and elevated aspartate aminotransferase (AST) levels. Jaundice is uncommon.
- Perihepatitis **(Fitz-Hugh-Curtis syndrome)** is a common complication of gonococcal infection that affects women almost exclusively. It is believed to result from direct spread of infection from the pelvis and does not affect overall outcome.
- It can also be caused by infection with Chlamydia trachomatis.

## Bacterial

- The sudden onset of sharp right upper quadrant pain, often following lower abdominal pain as an indicator of long-standing pelvic inflammatory disease, is typical. It may be confused with acute cholecystitis or pleurisy.
- This can be distinguished from gonococcal bacteremia by a characteristic **friction rub** over the liver and negative blood cultures. The diagnosis is made by vaginal cultures for N. gonorrhoeae.
- Laparoscopy may show characteristic **“violin-string”** adhesions between the liver capsule and the anterior abdominal wall.
- Treatment is with intravenous ceftriaxone.

# BURKHOLDERIA PSEUDOMALLEI (MELIOIDOSIS)

- This soil- and water-borne gram-negative bacterium that causes melioidosis is found predominantly in Southeast Asia and India.
- The clinical spectrum ranges from asymptomatic infection to fulminant septicemia.
- Severe disease involves the lung, gastrointestinal tract, and liver, with hepatomegaly and jaundice.
- Liver histologic changes include inflammatory infiltrates, multiple small and large abscesses, and focal necrosis.

## Bacterial

- Chronic disease is characterized by granulomas with central necrosis resembling tuberculous lesions. Organisms are rarely seen on Giemsa stains of liver biopsy specimens.
- The diagnosis can be made by serologic testing using an indirect hemagglutination assay.
- Initial antibiotic therapy consists of intravenous ceftazidime, imipenem, or meropenem.

# SHIGELLA AND SALMONELLA SPP.

- Cholestatic hepatitis can be attributable to enteric infection with Shigella species; liver histologic findings include portal and periportal polymorphonuclear infiltration, focal necrosis, and cholestasis.
- Typhoid fever caused by Salmonella typhi frequently involves the liver. Some patients may present with acute hepatitis, characterized by fever and tender hepatomegaly. Cholangitis, cholecystitis, and liver abscesses may occur.

## Bacterial

- Mild to moderate elevations of serum bilirubin (up to 16% of cases) and aminotransferase (up to 60%) levels are common in typhoid fever and should not prompt a search for a separate diagnosis.
- Hepatic damage appears to be mediated by bacterial endotoxin, which can produce nonspecific reactions, such as sinusoidal and portal inflammation, necrosis, hypertrophy of Kupffer cells, and non-necrotizing granulomas.
- Hepatic abnormalities do not appear to affect outcome and typically remit after 2 to 3 weeks of treatment with fluoroquinolones, third-generation cephalosporins, or ampicillin.

# YERSINIA ENTEROCOLITICA

- This infection manifests as ileocolitis in children and terminal ileitis and mesenteric adenitis in adults.
- Patients with hepatic involvement have underlying comorbidities such as diabetes mellitus, cirrhosis, or hemochromatosis; excess tissue iron appears to be a predisposing factor.
- The subacute septicemic form of the disease resembles typhoid fever or malaria. Multiple abscesses are diffusely distributed in the liver and spleen. The mortality rate approaches 50%.
- The granulomatous form produces noncaseating granulomas.

# ACTINOMYCES ISRAELII (ACTINOMYCOSIS)

- Actinomyces israelii is found worldwide in soil.
- Cervicofacial infection is the most frequent manifestation of actinomycosis, but gastrointestinal involvement is common (13% to 60% of cases).
- Hepatic involvement is present in 15% of cases of abdominal actinomycosis, most often as abscesses, and is thought to result from metastatic spread from other abdominal sites through the portal vein.
- The course is more indolent than that of other causes of pyogenic hepatic abscess. Abscesses may be multiple and in both lobes of the liver.
- The diagnosis is based on aspiration of an abscess cavity and visualization of characteristic “sulfur granules” or a positive anaerobic culture.
- Most abscesses resolve with a prolonged course of intravenous penicillin or oral tetracycline.

# BARTONELLA BACILLIFORMIS (BARTONELLOSIS, OROYA FEVER)

- This is endemic to Colombia, Ecuador, and Peru and is transmitted by infected sandflies.
- This acute febrile illness is accompanied by jaundice, hemolysis, hepatosplenomegaly, and lymphadenopathy.
- Centrilobular necrosis of the liver and splenic infarction may occur.
- Mortality rates resulting from sepsis or hemolysis approach 40%, but prompt treatment with chloramphenicol, fluoroquinolones, or tetracycline prevents fatal complications.

# BRUCELLA SPP. (BRUCELLOSIS)

- This may be acquired from infected pigs (Brucella suis), cattle (B. abortus), goats (B. melitensis), or sheep (B. ovis).
- It manifests as an acute febrile illness with arthralgias, headaches, and malaise or as subacute or chronic disease.
- Hepatomegaly and abnormal liver biochemical test levels are common; jaundice may be present in severe cases.
- Typically, liver histologic examination shows multiple noncaseating granulomas and, less often, focal portal tract infiltration or fibrosis.
- The diagnosis is confirmed by serologic testing in combination with an animal exposure history.
- Imaging reveals lesions with central calcification and a necrotic rim.
- A prolonged course of combination antimicrobial therapy with streptomycin, rifampin, and doxycycline is most effective.

# Rickettsial

# COXIELLA BURNETII (Q FEVER)

This is characterized by relapsing fevers, headache, myalgias, malaise, pneumonitis, and culture-negative endocarditis; the liver is commonly affected. The predominant abnormality is an elevated serum alkaline phosphatase level.

- The hepatic histologic hallmark is the intra-acinar granuloma with a central fat vacuole surrounded by fibrin ring and macrophages, the “fibrin-ring granuloma” or “doughnut lesion.”
- The diagnosis is confirmed by serologic testing for complement-fixing antibodies.
- Doxycycline is the treatment of choice.

# RICKETTSIA RICKETTSII (ROCKY MOUNTAIN SPOTTED FEVER)

- Mortality caused by this systemic tick-borne illness has decreased considerably as a result of early recognition; a few patients present with multiorgan manifestations and have a high mortality rate.
- Hepatic involvement is frequent in multiorgan Rocky Mountain spotted fever, predominantly as jaundice; pathologic examination reveals portal perivascular inflammation and vasculitis.
- Treatment with tetracycline should be initiated when infection is suspected.

# Spirochetal

# LEPTOSPIRA SPP. (LEPTOSPIROSIS)

- This is among the most common zoonoses in the world, with a wide range of domestic and wild animal reservoirs.
- Human-to-human transmission is uncommon.
- Up to 80% of the population has been exposed in some tropical countries; it is uncommon in the United States.
- Human disease can occur as one of two syndromes: anicteric leptospirosis and Weil's disease.

# LEPTOSPIRA SPP. (LEPTOSPIROSIS)

- **Anicteric leptospirosis** accounts for more than 90% of cases. It is characterized by a self-limited biphasic course. A few patients have elevated serum aminotransferase and bilirubin levels with hepatomegaly.
  - The first phase begins abruptly, with viral illness–like symptoms associated with fever, leptospiremia, and characteristic conjunctival suffusion (an important diagnostic clue) and lasts 4 to 7 days; leptospires are present in the blood or cerebrospinal fluid (CSF).
  - The second or immune phase, lasting 4 to 30 days, follows 1 to 3 days of improvement and is characterized by myalgias, nausea, vomiting, abdominal tenderness, and aseptic meningitis in up to 80% of patients.

# LEPTOSPIRA SPP. (LEPTOSPIROSIS)

- **Weil's disease** is a severe icteric form of leptospirosis and constitutes 5% to 10% of all cases.
- Complications are mainly the result of direct vascular damage by the Leptospira. The two phases of disease are less distinct:
  - The first phase is often marked by jaundice, which may last for weeks.
  - During the second phase, fever may be high, and hepatic and renal manifestations predominate. Jaundice is marked, with serum bilirubin levels approaching 30 mg/dL. Aminotransferase levels usually do not exceed five times the upper limit of normal, and thrombocytopenia is common. Acute tubular necrosis, which can lead to renal failure, cardiac arrhythmias, and hemorrhagic pneumonitis, are common. Mortality rates range from 5% to 40%.

# LEPTOSPIRA SPP. (LEPTOSPIROSIS)

- The diagnosis of leptospirosis is made on clinical grounds in conjunction with positive cultures of blood or CSF in the first phase or urine in the second phase.
- Isolation of the organism is difficult and may require many weeks. Microagglutination testing and serologic testing by (ELISA) may confirm the diagnosis in the second phase.
- Liver histologic examination reveals individual hepatocyte damage and canalicular cholestasis with mild portal inflammation.
- Doxycycline 200 mg per day is given in mild cases (effective only if given early) and as prophylaxis after exposure.
- Severe cases require intravenous penicillin, with a risk of a Jarisch-Herxheimer reaction. Most patients recover without residual organ impairment.

# TREPONEMA PALLIDUM (SYPHILIS)

## 1. Congenital syphilis

- Liver involvement may result from immunologic mechanisms and is worsened by penicillin treatment.
- Newborns have characteristic mucocutaneous lesions and osteochondritis, as well as hepatosplenomegaly and jaundice.
- Liver histologic examination reveals diffuse hepatitis with spirochetes seen mostly in the spaces of Disse.

# TREPONEMA PALLIDUM (SYPHILIS)

## 2. Secondary syphilis

- Liver involvement is characteristic (up to 50% of cases) and usually manifests with nonspecific symptoms. Jaundice, hepatomegaly, and right upper quadrant tenderness are less common. Nearly all patients exhibit generalized lymphadenopathy.
- Biochemical testing generally reveals low-grade elevations of serum aminotransferase and bilirubin levels, with a disproportionate elevation of the serum alkaline phosphatase level.
- Liver histologic examination reveals focal necrosis, especially in the periportal and centrilobular regions, or granulomas and portal vasculitis. Spirochetes may be demonstrated by silver staining in up to half of patients.
- Liver dysfunction may be worsened by the Jarisch-Herxheimer reaction as a response to treatment, which can occur with treatment of all spirochete infections.

# TREPONEMA PALLIDUM (SYPHILIS)

## 3. Tertiary (late) syphilis

- Hepatic lesions are common but typically silent. Occasionally, tender hepatomegaly and nodularity may raise the suspicion of metastatic cancer (hepar lobatum).
- If hepatic involvement is unrecognized, hepatocellular dysfunction and complications of portal hypertension can ensue.
- The characteristic lesions in tertiary syphilis are single or multiple gummas with central necrosis, often surrounded by granulation tissue consisting of a lymphoplasmacytic infiltrate with endarteritis obliterans. Exuberant deposition of scar tissue can ensue. Treponemes are rarely found.
- Treatment consists of benzathine penicillin G.

# BORRELIA BURGDORFERI (LYME DISEASE)

- This multisystem disease is caused by the tick-borne spirochete Borrelia burgdorferi.
- Predominant manifestations are dermatologic, cardiac, neurologic, and musculoskeletal.
- Hepatic involvement occurs in 20% of affected patients and usually manifests as hepatomegaly with increased serum aminotransferase and lactate dehydrogenase levels.
- In early stages, the spirochetes disseminate hematogenously from the skin and multiply in the organs of the reticuloendothelial system, including the liver. The clinical picture is suggestive of acute hepatitis and often accompanies erythema chronicum migrans, the sentinel rash.

# BORRELIA BURGDORFERI (LYME DISEASE)

- Liver histologic examination reveals hepatocyte ballooning, marked mitotic activity, microvesicular fat, hyperplasia of Kupffer cells, a mixed sinusoidal infiltrate, and intraparenchymal and sinusoidal spirochetes on Warthin-Starry stain.
- The diagnosis is confirmed by serologic testing in a patient with a typical clinical history.
- Hepatic involvement does not appear to affect overall outcome, which is excellent in primary disease after antibiotic treatment with doxycycline or penicillin.

# Parasitic Diseases that Involve the Liver

# 1- Amebic liver abscess

## OVERVIEW

- Worldwide, 480 million people are infected with Entamoeba histolytica.
- Amebic infection may be asymptomatic or may manifest as dysentery, hepatic amebic abscess, or other (rarer) manifestations.
- The diagnosis and management of hepatic amebic abscess have been revolutionized by advances in imaging and interventional radiology.
- Treatment now relies almost entirely on drug therapy.

# Amebic liver abscess

## PARASITOLOGY

- Amebic liver abscess is caused by the protozoan E. histolytica.
- The reservoir of infection is human.
- The infective form is the cyst (12 μm in diameter), which is ingested.
- Excystation occurs in the small intestine. The trophozoite (10 to 60 μm) infects the colon and may cause inflammation and dysentery.
- Amebae spread to the liver through the portal circulation.
- The cyst is able to survive outside the body for weeks or months, whereas the trophozoite degenerates in minutes.
- Amebae may be pathogenic or nonpathogenic. The nonpathogenic form has been reclassified as Entamoeba dispar. Pathogenic species can be differentiated from nonpathogenic species by the following:
  - Zymodene analysis: 22 distinct isoenzyme patterns (zymodenes) on electrophoresis have been isolated
  - n RNA and DNA probes

# Amebic liver abscess

## EPIDEMIOLOGY

- Infection with E. histolytica affects 10% of the world's population; 40 to 50 million people develop amebic colitis or amebic liver abscess, and 40,000 to 100,000 deaths occur per year.
- The prevalence of infection varies from less than 1% in industrialized countries to 50% to 80% in some tropical regions, and it has been found to be 100% in an area of The Gambia.
- Spread is by the fecal-oral route and is increased by the following:
  - Poor sanitation
  - Contamination of food by flies
  - Unhygienic food handling
  - Unclean water
  - Use of human feces as fertilizer

# Amebic liver abscess

**High-risk groups are as follows:**

- Persons of lower socioeconomic status in endemic areas.
- Immigrants from endemic areas.
- Institutionalized populations (e.g., inpatients of psychiatric hospitals).
- Men who have sex with men.
- Travelers.
- Persons who are immunosuppressed, including those with human immunodeficiency virus (HIV) infection.

# Amebic liver abscess

## PATHOGENESIS

- In the liver, E. histolytica lyses the host's tissue with proteolytic enzymes contained in cytoplasmic vacuoles.
- The hepatic lesion is a well-demarcated abscess consisting of necrotic liver and usually affecting the right lobe.
- The initial host response to the ameba is neutrophil migration, but the ameba can also lyse neutrophils, thus releasing their enzymes and assisting in the process of tissue destruction.
- The abscess contains acellular debris; amebic trophozoites are found only at the periphery of the lesion, where they can invade further.

# Amebic liver abscess

## PATHOGENESIS

- The following host factors contribute to the severity of disease:
  - Age (children more than adults)
  - Pregnancy
  - Malnutrition and alcoholism
  - Corticosteroid use
  - Malignant disease

# Amebic liver abscess

## CLINICAL FEATURES

- Amebic liver abscess manifests with amebic colitis in only 10% of cases.
- Among patients, 20% have a past history of diarrhea or dysentery.
- E. histolytica can be isolated from the stool in approximately 50% of cases.

1. **History**: socioeconomic and demographic

- Emigrant from or resident in an endemic area
- Traveler to an endemic area
- Men more than women (3 to 10 times)
- Young adults more than children or elderly persons

# Amebic liver abscess

## CLINICAL FEATURES

### 2. Symptoms

- Fever, rigors, night sweats
- Nausea, anorexia, malaise
- Right upper quadrant abdominal discomfort
- Weight loss
- Chest symptoms: dry cough, pleuritic pain
- Diaphragmatic irritation: shoulder tip pain, hiccups

### 3. Physical examination

- Fever
- Tender hepatomegaly
- Chest signs: dull right base (usually from raised hemidiaphragm); crackles at right base; pleural rub
- Jaundice and peritonitis or pericardial rub: rare; poor prognostic signs

# Amebic liver abscess

## 1. Laboratory findings

Increased serum bilirubin level is uncommon.

TABLE 28.1 ■ **Laboratory findings in amebic liver abscess**

| Laboratory finding | Frequency (%) |
|---|---|
| Leukocytosis | 80 |
| Elevated serum alkaline phosphatase level | 80 |
| Anemia | >50 |
| Increased erythrocyte sedimentation rate | Common |
| Proteinuria | Common |
| Elevated serum aminotransferase levels | Poor prognostic sign |

# Amebic liver abscess

## 2. Diagnostic imaging

### a. Chest radiograph:

- Elevation of right hemidiaphragm
- Blunting of right costophrenic angle
- Atelectasis

### b. Ultrasonography

- Round or oval single lesion (sometimes multiple)
- Lack of significant wall echoes, so the transition from abscess to normal liver is abrupt
- Hypoechoeic appearance compared with normal liver; diffuse echoes throughout abscess
- Peripheral location, close to liver capsule
- Distal enhancement

# Amebic liver abscess

**c. Computed tomography (CT)**

- Well-defined lesions, round or oval, mostly single (sometimes multiple)
- Low density compared with surrounding liver tissue
- Nonhomogeneous internal structure

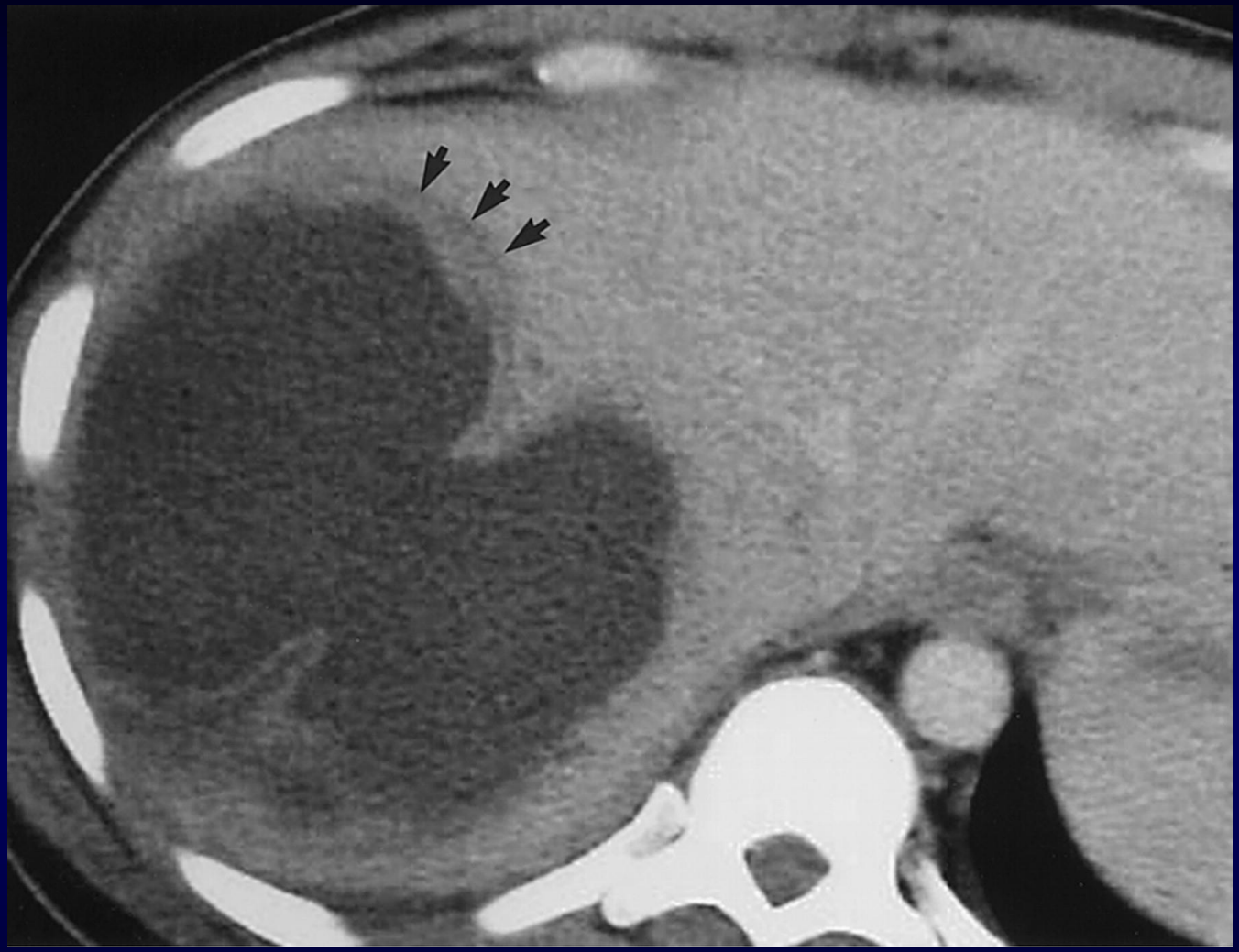
**d. Magnetic resonance imaging (MRI)**

- Abscess characterized by low signal intensity on T1-weighted images and high signal intensity on T2-weighted images

**e. Radionuclide imaging**

- Amebic liver abscess appears as a cold spot, apparently distinguishing it from pyogenic abscess; this modality has not been researched extensively for this use

# Amebic abscess.



Amebic abscess. Contrast-enhanced CT scan demonstrates a large, lobulated, well-defined cystic mass in the right hepatic lobe. Note the enhanced, thickened wall of the lesion (arrows).

# Amebic liver abscess

## 3. Serologic tests:

The detection of antibodies is the mainstay of diagnosis of invasive amebiasis. Available assays include the following:

**a. Indirect hemagglutination**

- Sensitivity of 90% to 100%
- Raised titers may persist for more than 2 years.

**b. Gel diffusion**

- Useful for differentiating recent from past infection because result remains positive for only 6 to 12 months after the onset of infection

**c. Counterimmunoelectrophoresis**

- Cellulose acetate precipitation test (CAP) is highly sensitive and specific; becomes negative quickly after successful treatment; regarded as a reference test for amebic serology

**d. Complement fixation**

**e. Enzyme-linked immunosorbent assay**

- Sensitivity and specificity as high as 97.9% and 94.8%, respectively

These tests are positive in all forms of invasive amebic disease (including dysentery). Combined testing may be necessary for accurate diagnosis.

# Amebic liver abscess

## 4. Aspiration of abscess

(when diagnosis is uncertain or for imminent rupture)

- Yellow to dark brown “anchovy sauce”.
- Odorless.
- “Pus” consisting mainly of acellular debris; most amebae found in abscess wall.

# Amebic liver abscess

## COMPLICATIONS

**1.Rupture of abscess into the following:**

a. **Chest, causing**
   - Hepatobronchial fistula (± expectoration of "anchovy" pus)
   - Lung abscess
   - Amebic empyema

b. **Pericardium, causing**
   - Heart failure
   - Pericarditis
   - Cardiac tamponade (often fatal; may be followed by constrictive pericarditis)

c. **Peritoneum, causing**
   - Peritonitis
   - Ascites

# Amebic liver abscess

## COMPLICATIONS

2. **Secondary infection is usually iatrogenic following aspiration.**
3. **Other complications (rare):**
   - Fulminant hepatic failure
   - Hemobilia
   - Inferior vena cava obstruction
   - Budd–Chiari syndrome
   - Hematogenous spread causing cerebral abscess
4. **Factors predisposing to complications:**
   - Age greater than 40 years
   - Concomitant corticosteroid use
   - Multiple abscesses
   - Large abscess more than 10 cm in diameter
   - Erythrocyte sedimentation rate (ESR) and C-reactive protein level are reported to be very high in patients who present with or go on to develop systemic complications.

# Amebic liver abscess

## TREATMENT AND PROGNOSIS

(Treatment of amebic liver abscess is usually with drugs alone)

**1. Commonly used regimens (administered orally):**

- Metronidazole 750 mg three times daily for 5 to 10 days (pediatric, 35 to 50 mg/kg per day in three divided doses for 5 days), or
- Tinidazole 2 g/day (pediatric, 50 to 60 mg/kg daily for 5 days) for 3 days, or
- Chloroquine 1 g loading dose for 1 to 2 days, then 500 mg/day (pediatric, 10 mg/kg base) for 20 days.

# Amebic liver abscess

## TREATMENT AND PROGNOSIS

**2. Luminal amebicides must always be used following the aforementioned regimens:**

- Diloxanide furoate 500 mg three times daily (pediatric, 20 mg/kg per day in three divided doses) for 10 days, or
- Diiodohydroxyquin 650 mg three times daily (pediatric, 30 to 40 mg/kg per day in three divided doses; maximum 2 g/day) for 20 days, or
- Paromomycin sulfate 25 to 35 mg/kg/day in three divided doses (pediatric, 25 to 35 mg/kg per day in three divided doses) for 5 to 10 days

# Amebic liver abscess

## TREATMENT AND PROGNOSIS

### 3. Optimal management

- Patients with suspected amebic abscess should be started on therapy while awaiting serologic confirmation. Response is usually rapid, with defervescence occurring in 48 to 72 hours.
- Critically ill patients, those with left lobe abscess, or those who do not respond to initial drug therapy may require radiologically guided fine-needle aspiration to avoid rupture and to exclude a pyogenic abscess.
- Complications such as rupture of the abscess may be managed medically but often require percutaneous drainage. Surgical drainage is seldom required.

# Amebic liver abscess

## PROGNOSIS

- Amebic liver abscess is an eminently treatable condition.
- The mortality rate is less than 1% in uncomplicated disease.
- Delay in diagnosis may result in abscess rupture, with a higher mortality rate:
  1. Rupture into chest or peritoneum: 20% mortality rate
  2. Rupture into pericardium: 32% to 100% mortality rate

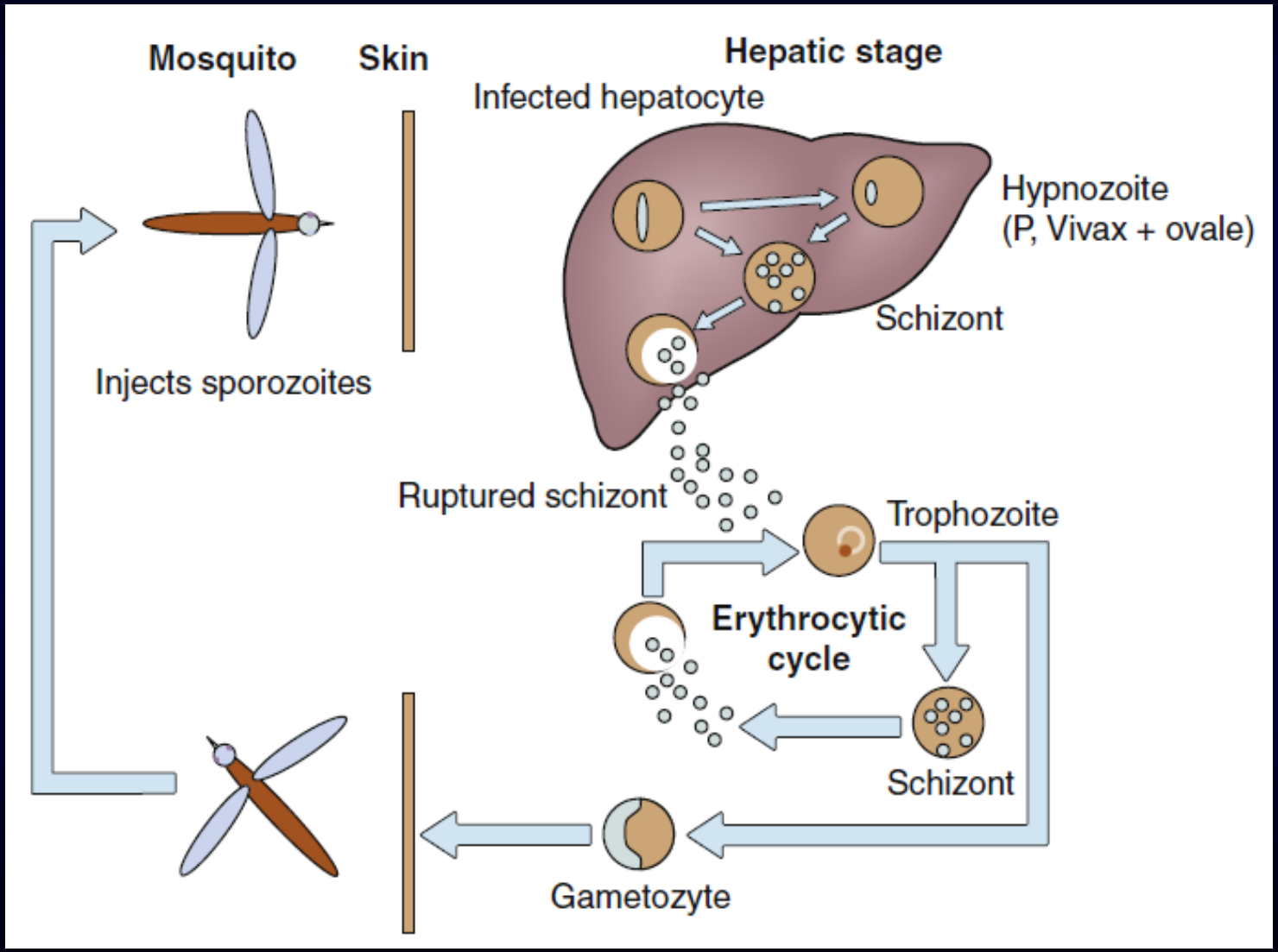
# 2- Malaria

Malaria is one of the most important public health problems worldwide, annually infecting about 300 to 500 million persons in more than 100 countries and causing at least 1 million deaths.

## Life cycle:

- The liver is affected during two stages of the malarial life cycle; the pre-erythrocytic phase and the erythrocytic phase, during which symptoms are noted.

# Malaria


Mosquito
Skin
Hepatic stage
Infected hepatocyte
Hypnozoite
(P, Vivax + ovale)
Schizont
Injects sporozoites
Ruptured schizont
Trophozoite
Erythrocytic
cycle
Schizont
Gametozyte

# Malaria

- The extent of hepatic injury varies with malarial species (most severe with P. falciparum) and severity of infection.
- Unconjugated hyperbilirubinemia is most commonly seen as a result of hemolysis, but occasional hepatocyte dysfunction can be seen, leading to conjugated hyperbilirubinemia as well as a prolonged prothrombin time.
- Reversible reductions of portal venous blood flow during the acute phase of falciparum malaria may be a consequence of microocclusion of portal venous branches by parasitized erythrocytes.

# Malaria

## Histopathology

- In an acute attack of falciparum malaria, large quantities of malarial pigment, hemozoin (an iron porphyrin protein complex resulting from hemoglobin degradation by the parasite) accumulates in Kupffer cells, which hypertrophy and phagocytose erythrocytes. Sinusoidal dilatation also occurs.
- Later, a mild portal infiltrate and portal pigment deposition occurs.
- All abnormalities reverse with successful treatment.

# Malaria

## Clinical features

- Only the erythrocytic stage of malaria is associated with clinical illness.
- Symptoms develop 30 to 60 days after exposure to an infected mosquito and include cyclical fever, malaise, anorexia, nausea, vomiting, diarrhea, and myalgias.
- Tender hepatomegaly and splenomegaly, as well as jaundice caused by hemolysis, are common in adults, especially with heavy infection by P. falciparum.
- Hepatic failure is generally seen only in association with concomitant viral hepatitis or with severe P. falciparum infection.

# Malaria

## Differential diagnosis

- The differential diagnosis includes hepatotropic and nonhepatotropic viral hepatitis, gastroenteritis, amebic liver abscess, yellow fever, typhoid fever, tuberculosis, leptospirosis, and brucellosis.

# Malaria

## Diagnosis

- The diagnosis of acute malaria rests on clinical history, physical examination, and identification of parasites on peripheral thick or thin blood smears.
- Because the number of parasites in the blood may be small, repeated smear examinations should be performed when the index of suspicion is high.
- Serologic assays are less useful for acute than for chronic infection.

# Malaria

## Treatment

- Treatment depends on the species and the pattern of chloroquine resistance for falciparum infection.
- In general, chloroquine is effective for P. malariae, P. vivax, P. ovale, and P. falciparum in areas endemic for chloroquine-sensitive species.
- Resistant falciparum infections can be treated with atovaquone/proguanil, or quinine in combination with doxycycline, tetracycline, or clindamycin, or artemether/lumefantrine, or artesunate alone.
- For P. vivax and P. ovale infections, treatment with primaquine (in persons without glucose-6-phosphate dehydrogenase deficiency) is indicated to eliminate the exoerythrocytic hypnozoites in the liver.

# 3- Babesiosis

- This is caused by Babesia species and is transmitted by the deer tick Ixodes dammini/scapularis.
- This malaria-like illness is endemic to the Northeast and Midwest of the United States.
- Patients present with fever, anemia, hepatosplenomegaly, and abnormal liver biochemical test levels.
- Immunocompromised or asplenic patients are often affected more severely.
- Combination therapy with atovaquone 750 mg twice daily and azithromycin 500 mg followed by 250 mg once daily or with clindamycin 600 mg three times daily and quinine 650 mg three to four times daily for 7 days is recommended.

# 4- Leishmaniasis

- Visceral leishmaniasis is caused by Leishmania species, mostly L. donovani, and is endemic in the Mediterranean, the Middle East, Asia, Africa, and Latin America.

## Life cycle

- The parasite multiplies in the gut of the female sandfly as a flagellated promastigote and migrates to the pharynx.
- Following injection into the human host, promastigotes are phagocytosed by macrophages in the reticuloendothelial system, where they multiply as amastigotes and are taken up with the next blood meal of the sandfly.

# Leishmaniasis

## Clinical features

- Among early infections, 60% to 95% are subclinical.
- Visceral infection begins with a papular or ulcerative skin lesion at the site of the sandfly bite (similar to the cutaneous form of the disease).
- Following an incubation period of 2 to 6 months, twice daily fevers, weight loss, diarrhea (of bacillary, amebic, or leishmanial origin), and progressive painful hepatosplenomegaly develop, often accompanied by pancytopenia and polyclonal hypergammaglobulinemia.
- Liver biochemical test levels are typically normal.

# Leishmaniasis

- Secondary bacterial infections resulting from infiltration and suppression of reticuloendothelial cell function include pneumonia, pneumococcal infection, and tuberculosis and are important causes of mortality.
- Physical findings include often massive hepatomegaly, soft and nontender splenomegaly, jaundice, or ascites in severe disease, as well as generalized lymphadenopathy and muscle wasting.
- Cutaneous gray hyperpigmentation, which prompted the name kala-azar (“black fever”), is characteristically seen in India. Oral and nasopharyngeal nodules resulting from granuloma formation can be seen in Africa.

# Leishmaniasis

## Histopathology

- Organisms are found in macrophages of the liver and spleen, bone marrow, and lymph nodes.
- Occasionally, parasite-bearing cells aggregate within noncaseating granulomas.
- Hepatocyte necrosis is mild compared with that seen in cutaneous leishmaniasis.
- Healing is accompanied by fibrous deposition similar to that seen in congenital syphilis, and occasionally the liver looks cirrhotic (Rogers' cirrhosis).
- Complications of cirrhosis are rare.

# Leishmaniasis

## Diagnosis

- This is based on history, physical examination, and demonstration of tissue amastigotes.
- The demonstration of parasites or parasitic DNA in tissue is diagnostic.
- The highest yield comes from aspiration of the **spleen**, with parasites seen in 95% of cases.
- **Liver** aspiration is safer and has 70% to 85% sensitivity, as does bone marrow aspiration.
- **Lymph node** aspiration has 60% sensitivity.
- Serologic testing by ELISA or direct agglutination can be used to support a presumptive diagnosis of visceral leishmaniasis with 95% sensitivity and specificity.
- The leishmanin skin test (Montenegro test) is typically negative and unhelpful in acute visceral disease.

# Leishmaniasis

## Treatment

- No specific measures are necessary to treat hepatic involvement.
- Treatment of secondary bacterial infections is essential, and specific antileishmanial chemotherapy should be initiated promptly.
- Liposomal amphotericin B is approved for treatment. Sodium stibogluconate (Pentostam) is available through the Centers for Disease Control and Prevention (CDC) under an investigational protocol.
- Alternative agents include paromomycin and pentamidine, which has significant toxicity.
- Patients with acquired immunodeficiency syndrome (AIDS) and leishmaniasis often fail to respond or relapse following treatment with conventional regimens.

# 5- Toxoplasmosis

- Infection caused by Toxoplasma gondii is found worldwide.
- In the United States, serologic surveys suggest that 20% to 40% of the population have been exposed to T. gondii, resulting in chronic or latent infection.
- Toxoplasmosis causes clinical disease either when transmitted congenitally or as an opportunistic infection complicating AIDS.

# Toxoplasmosis

## Life cycle

- Cats are the definitive hosts; humans and other animals are incidental hosts that become infected by ingestion of oocysts.
- The oocysts mature in the intestinal tract of humans to become sporozoites, which penetrate the intestinal mucosa, become tachyzoites, and circulate systemically, thus invading a wide array of cell types.
- They can form tissue cysts, containing many bradyzoites, which are responsible for latent infection.
- Hepatic involvement has been observed in severe, disseminated infection.

# Toxoplasmosis

## Clinical features

- Acquired toxoplasmosis can manifest as a mononucleosis-like illness with fever, chills, headache, and lymphadenopathy.
- Uncommonly, hepatomegaly, splenomegaly, and minimal elevations of serum aminotransferase levels are present.
- Infection of immunocompromised hosts can result in encephalitis, chorioretinitis, pneumonitis, myocarditis, and, uncommonly, hepatitis.
- Atypical lymphocytosis, an otherwise unusual feature of parasitic disease, may occur.

# Toxoplasmosis

## Diagnosis

- This is best made by detecting specific IgM or IgG antibody using indirect immunofluorescence or an enzyme immunoassay (EIA) and isolation of T. gondii from blood, body fluids, or tissue.

## Treatment

- Antibiotic therapy (pyrimethamine 25 to 100 mg daily and sulfadiazine 1 to 1.5 g four times daily), plus folinic acid to minimize hematologic toxicity, for 3 to 4 weeks, should be administered to immunocompetent persons with severe infection and immunocompromised or pregnant patients.

# HELMINTHIC INFECTIONS

# Hydatid Disease of the Liver

## Overview

- Hydatid cystic disease has a worldwide distribution and is endemic in many sheep- and cattle-rearing regions of the world.
- Hydatid disease is a chronic and potentially dangerous condition that is often overlooked as a cause of abdominal pain and hepatic disease.

# Hydatid Disease of the Liver

## Parasitology

- Hydatid cystic disease is caused by Echinococcus granulosus.
- E. granulosus is a 3- to 6-mm tapeworm.
- A carnivorous host, usually a dog, becomes infected by eating the viscera of infected sheep that contain hydatid cysts.
- Scolices from the cysts adhere to the small intestine of the dog and develop into the tapeworm.
- The tapeworm produces up to 500 ova in the host bowel.
- Infected dogs excrete Echinococcus eggs in feces.
- Eggs are viable in the environment for several weeks.

# Hydatid Disease of the Liver

## Parasitology

- Eggs are ingested by humans, either from contamination of soil and foodstuffs or from the dog's coat, and they hatch in the intestine to form oncospheres that invade tissue to enter the portal circulation.
- Each oncosphere matures into a vesicle and subsequently a cyst, the metacestode.
- Cysts can form in any organ, most commonly the liver (50% to 70%).
- Cysts consist of a germinal layer that buds asexually to form daughter cysts, which contain protoscolices, the infective forms that are ingested by the definitive host.

# Hydatid Disease of the Liver

## Pathogenesis

- Spread of oncospheres is through the bloodstream, usually the portal circulation, and results in hepatic disease in 50% to 70% of cases.
- Other sites of disease are as follows:
  - Lung (20% to 30%)
  - Bone (less than 10%)
  - Brain
  - Heart
- Cysts enlarge slowly and cause tissue damage directly or by compromising the blood supply.
- The parasite causes a host response to form a collagenous capsule around the germinal layer. This capsule may calcify.
- Often, no host inflammatory response occurs.

# Hydatid Disease of the Liver

## Clinical features

- Symptoms

TABLE 28.4 ■ **Clinical features of 650 patients with a liver hydatid cyst**

| Feature | Number (%) |
|---|---|
| Abdominal pain | 435 (66.9%) |
| Fullness in the upper abdomen and dyspepsia | 234 (36.0%) |
| Hepatomegaly | 201 (30.9%) |
| Asymptomatic | 182 (28.0%) |
| Jaundice | 104 (16.0%) |
| Mass in the right upper quadrant | 39 (6.0%) |
| Acute abdomen | 13 (2.0%) |

# Hydatid Disease of the Liver

- Cysts may be asymptomatic and often become symptomatic only after decades, because of their slow growth. Symptoms are caused by pressure effects.
- Symptoms may follow cyst rupture or leakage.
- The presentation of a secondary infection of a hydatid cyst resembles the presentation of a pyogenic abscess.
- Physical examination
  - Tender mass
  - Chest signs, especially at the right base
  - Fever
  - Jaundice

# Hydatid Disease of the Liver

## DIAGNOSIS

- Laboratory findings
  - Elevated serum alkaline phosphatase level
  - Peripheral eosinophilia (>7%) in 30% of patients, usually indicating leakage or rupture of cyst
  - Elevated serum bilirubin level (uncommon)
- Diagnostic imaging

1. **Chest x-ray**
   - Elevation of the right hemidiaphragm
   - Cysts may be visible in the lung
   - Calcification of hepatic cyst may be visible below the diaphragm

# Hydatid Disease of the Liver

## DIAGNOSIS

### 2. Ultrasonography

- Cysts may be anechoic
- Typically round
- Septate or daughter cysts are often visible
- Separation of germinal membrane: “water-lily sign”
- Collapsed cysts may be visible
- Calcification of wall
- Hydatid “sand”

### 3. CT

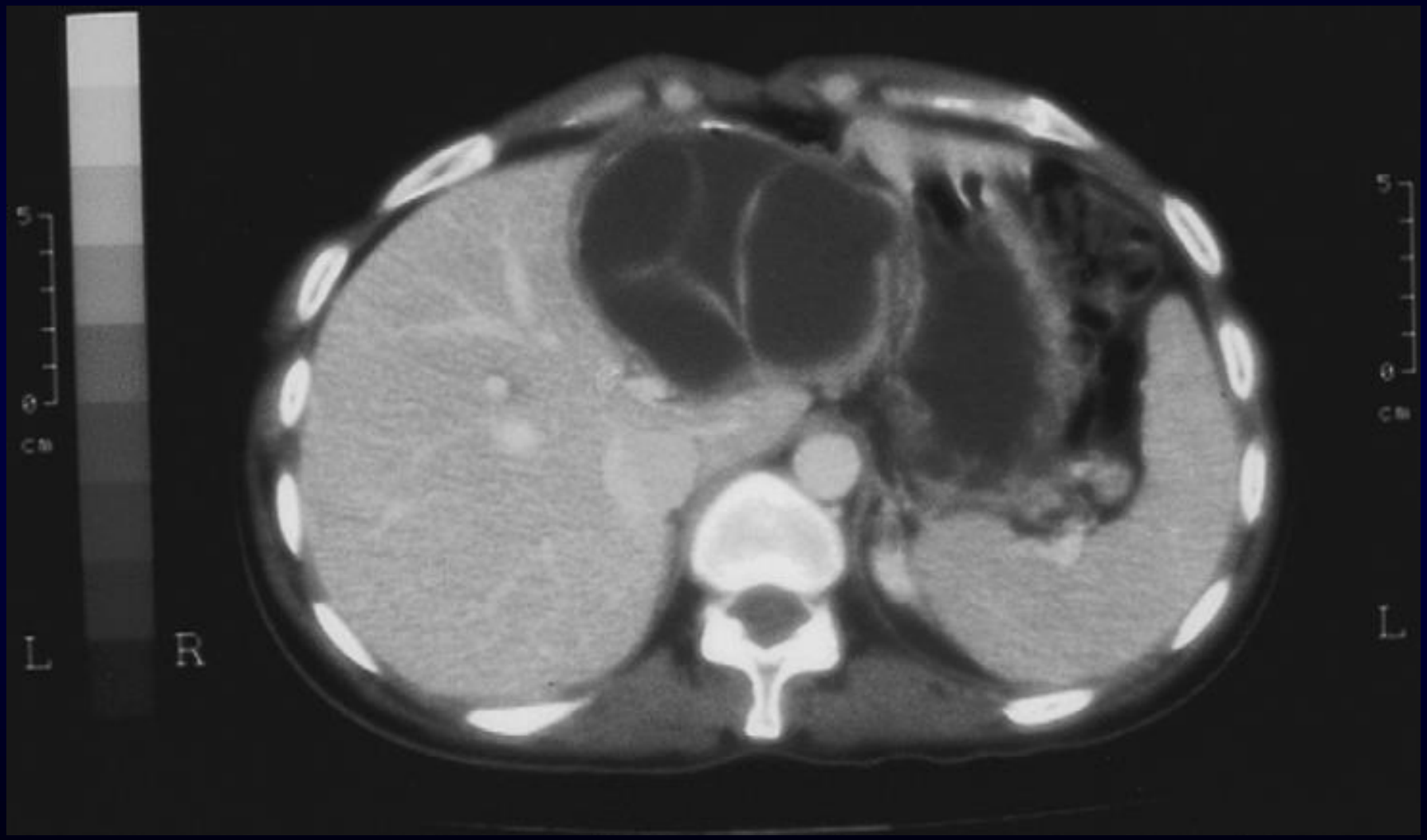
- Germinal layer seen clearly
- Daughter cysts readily visualized
- Lesion of low attenuation: 3 to 30 Hounsfield units

# Hydatid disease.

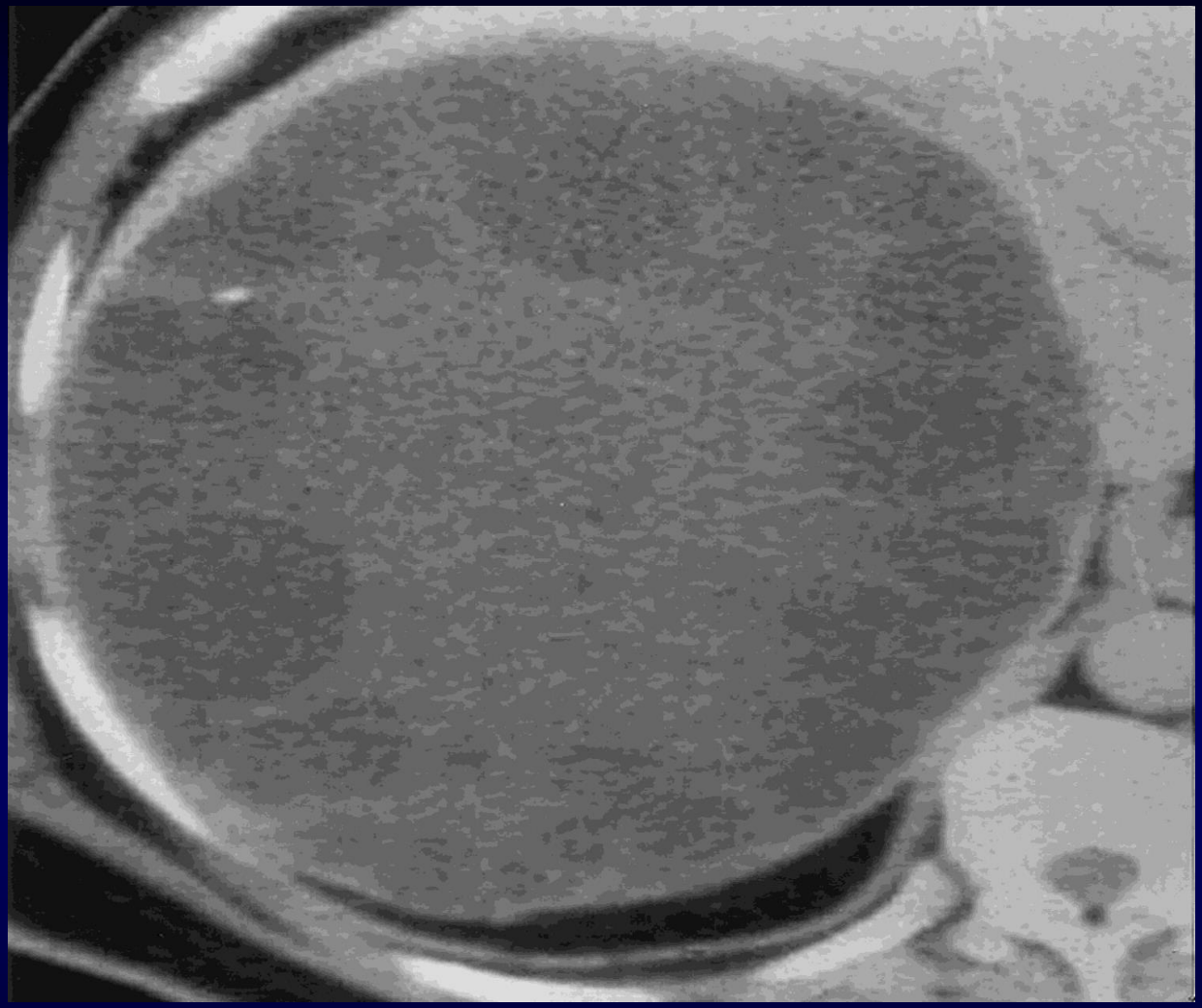
Hydatid disease. Longitudinal US image of the liver shows a rounded, well-defined, multilocular hypoechoic lesion with echogenic internal septa (arrows).

Helminthic

# Hydatid Disease of the Liver

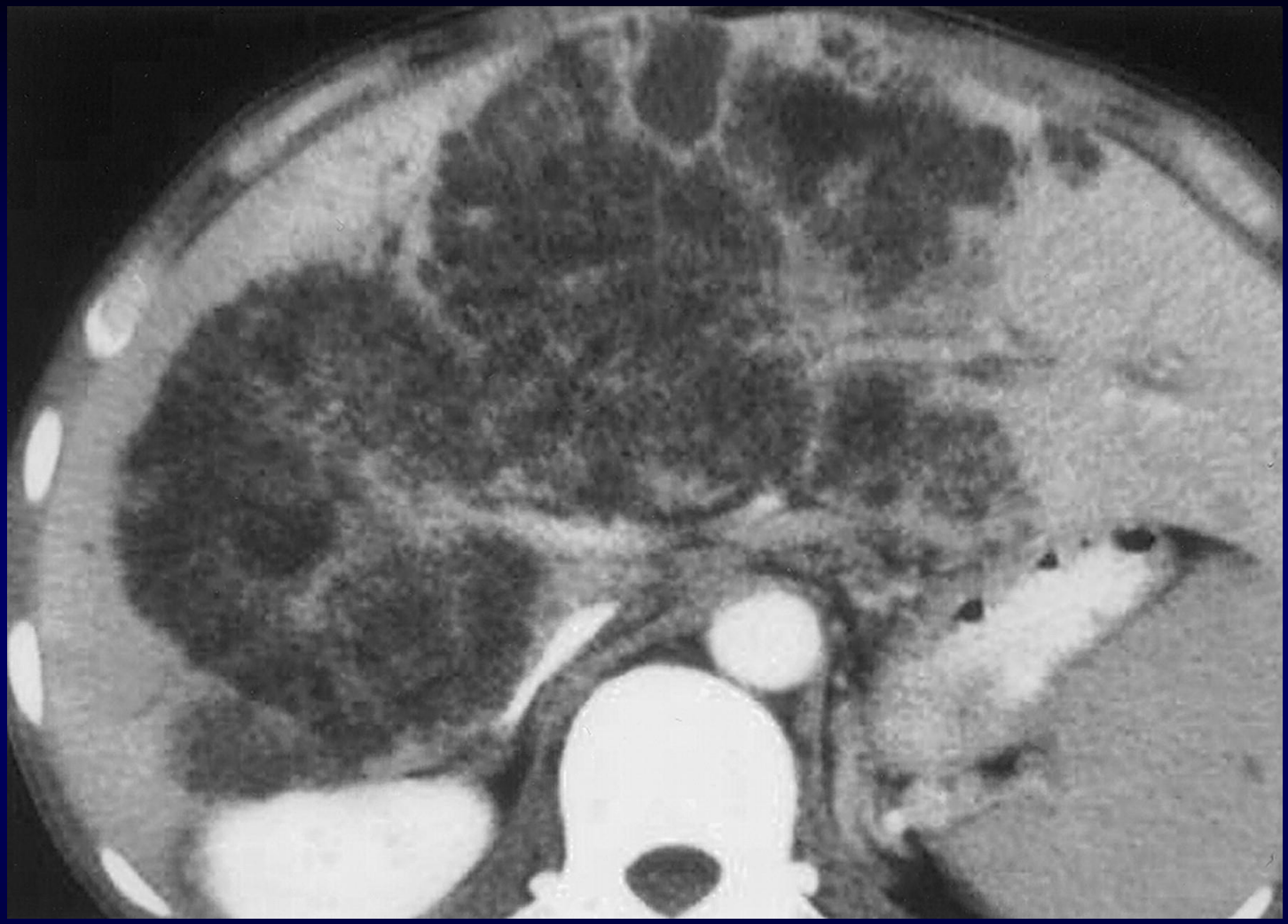


# Hydatid disease.



Hydatid disease. Unenhanced CT scan obtained in a different patient shows a large, multilocular hydatid cyst in the right hepatic lobe with multiple daughter cysts at the periphery. Note the hyperattenuating appearance of the matrix.

# E multilocularis.

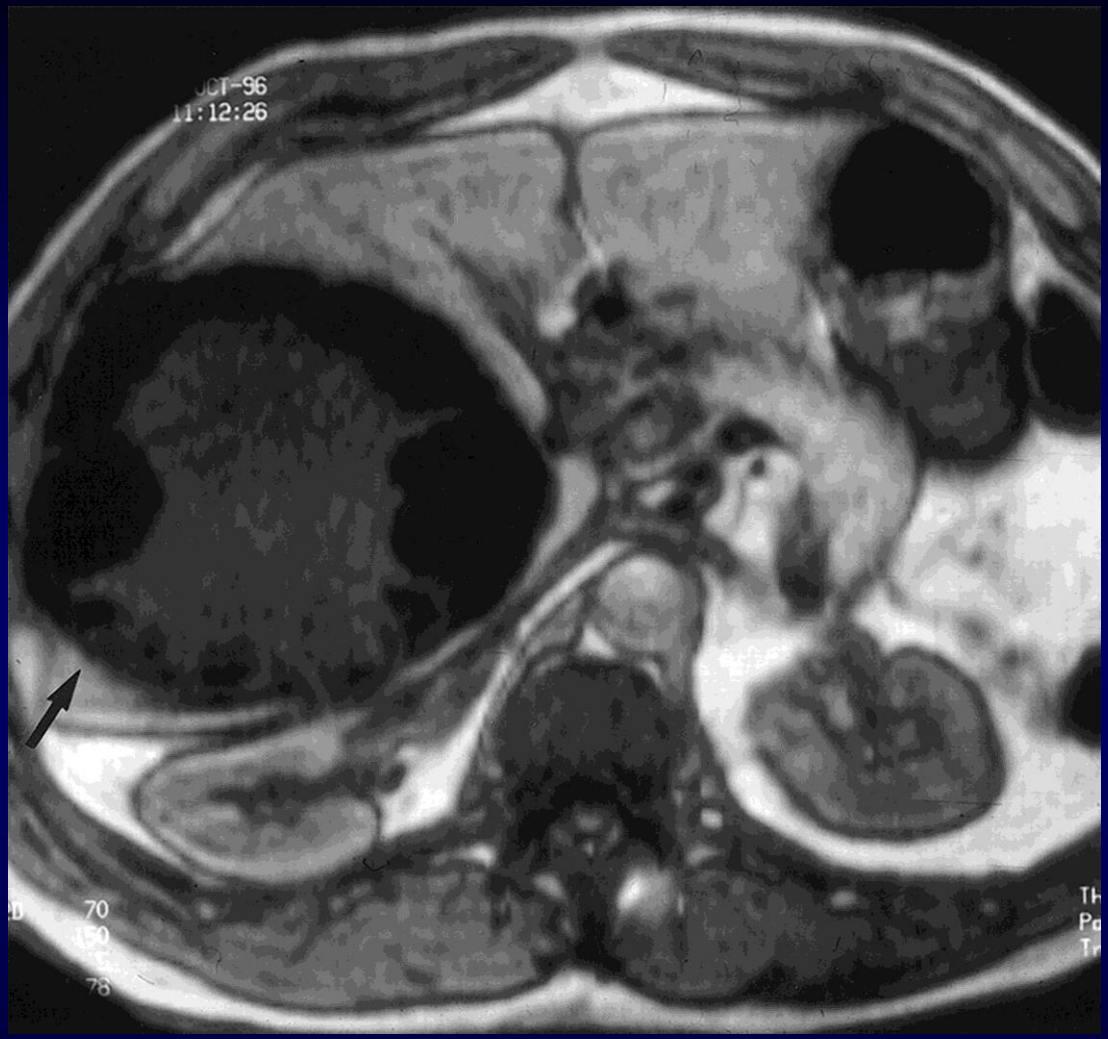


CT scans of the liver reveal a large, irregularly shaped, hypoattenuating lesion with diffuse punctate calcifications, which are more clearly seen on the unenhanced image. Note the poor enhancement of the lesion after bolus administration of contrast material.

# Hydatid Disease of the Liver

4. **MRI**
   - Characteristic low-intensity rim 4 to 5 mm thick, best seen on T2-weighted images
   - Lesion center nonhomogeneous
   - Lesion is hypointense on T1-weighted images, hyperintense on T2-weighted images
- Serologic tests:
  - Indirect haemagglutination (IHA) and enzyme-linked immunosorbent assay (ELISA) are 75% to 94% sensitive.
  - Specificity is lower, necessitating a confirmatory test (e.g., molecular biologic methods or immunoblotting).
- Molecular biologic tests:
  - Polymerase chain reaction (PCR)–derived probes allow diagnosis and species differentiation.

# Hydatid disease.



Axial gradient-echo T1-weighted MR image shows a hydatid cyst with a hypointense fibrous pericyst (arrow). The hydatid matrix has intermediate signal intensity, and peripheral daughter cysts that are hypointense relative to the matrix are seen.

# Hydatid Disease of the Liver

## COMPLICATIONS

1. Leakage or rupture of cyst (sometimes iatrogenic from aspiration of undiagnosed hydatid cyst) may result in the following:
   - Allergic reaction, including anaphylaxis (may be fatal)
   - Dissemination of disease
   - Cholangitis if cyst ruptures into the biliary tract
   - Hemoptysis and secondary infection if bronchial rupture
2. Secondary infection of cyst behaves like a pyogenic abscess.

# Hydatid Disease of the Liver

## TREATMENT AND PROGNOSIS

- **Surgery** remains the mainstay of treatment.
  - Regardless of the type of surgical technique employed, the combination of surgery with chemotherapy is the safest and most effective approach.
  - Hydatid cysts manifesting with secondary infection should be treated as pyogenic abscesses; however, aspiration of an infected hydatid cyst is more hazardous than is aspiration of a pyogenic abscess.

# Hydatid Disease of the Liver

## TREATMENT AND PROGNOSIS

- **Drug** therapy includes the following:
  - Albendazole 10 to 14 mg/kg/day orally for 3 months initially (may continue for 1 year) or
  - Mebendazole 30 to 70 mg/kg/day orally for 3 months (may require up to 200 mg/kg per day)
  - These benzimidazole agents act on the germinal layer.
  - Praziquantel (40 mg/kg orally per day for 14 days) has been used as a protoscolicide and, as such, has an important role preoperatively.

# Hydatid Disease of the Liver

## TREATMENT AND PROGNOSIS

- **Surgical** and **radiologic** options include the following:
  - Radical surgery: pericystectomy or hepatic resection
  - Conservative surgical treatment through unroofing and management of the residual cavity
  - Laparoscopic procedures
  - Percutaneous techniques, including puncture, aspiration, injection, reaspiration (PAIR)

# Hydatid Disease of the Liver

## TREATMENT

- The technique chosen depends on the condition of the patient, characteristics of the cyst, and experience of the surgeon or radiologist.
- The complication rate of surgery may be high. For example, 57% in a series of 59 patients had dissemination of infection, secondary infection, fistula formation, or complications from seepage of scolicidal agents into the biliary tract (causing a syndrome resembling sclerosing cholangitis).

## PROGNOSIS

- Hydatid cysts may remain asymptomatic throughout a person's life.
- Cyst rupture or infection is associated with considerable mortality.

# Ascariasis

- Ascaris lumbricoides is estimated to infect approximately 25% of the world's population, especially in tropical countries and areas of lower socioeconomic standing.

## Life cycle

- Humans are infected by ingesting embryonated eggs, usually in raw vegetables.
- The larvae hatch in the duodenum and migrate to the cecum, where they penetrate the mucosa, enter the portal circulation, and reach the liver, pulmonary artery, and lungs.
- The larvae grow in the alveolar spaces, are regurgitated and swallowed, and become mature adults in the intestine 2 to 3 months after ingestion, eventually reaching 15 to 35 cm, whereupon the cycle repeats itself.

# Ascariasis

## Clinical features

- Most infected persons are asymptomatic or minimally symptomatic during larval migration. Symptoms are generally proportionate to the worm burden.
- Cough, fever, dyspnea, wheezing, and substernal chest discomfort have been reported in the first 2 weeks of infection, as has hepatomegaly, when the larvae pass through the liver.
- Chronic infection is more frequently characterized by episodic epigastric or periumbilical pain.
- If the worm burden is particularly heavy, small bowel obstruction, intussusception, volvulus, perforation, or appendicitis may occur.

# Ascariasis

## Clinical features

- Fragments of disintegrating worms within the biliary tree can serve as a nidus for biliary calculus formation.
- Preexisting disease of the biliary tract or pancreatic duct can predispose to worm migration into the bile ducts, with resulting obstructive jaundice, cholangitis, cholecystitis, pancreatitis, or pylephlebitis and intrahepatic abscesses.

# Ascariasis

## Diagnosis

- In the absence of a history of worm passage or regurgitation, the diagnosis is made definitively by identification of characteristic eggs in stool specimens.
- Larvae have also been identified in sputum and gastric washings.
- Liver biopsy specimens may show granulomas surrounding typical eggs.
- Patients with biliary or pancreatic symptoms can be evaluated by ultrasonography or by endoscopic techniques, either retrograde cholangiopancreatography (ERCP) or direct choledochoscopy, which may identify the parasite and permit extraction of the worm.

# Ascariasis

## Treatment

- Infected persons may be treated with a single dose of albendazole 400 mg, mebendazole 100 mg twice daily for 3 days, or ivermectin 200 μg/kg × 1 dose.
- In patients with intestinal obstruction, piperazine citrate may be used (75 mg/kg for 2 days to a maximum of 3.5 g in adults and 2 g in children under 20 kg). This agent paralyzes the worm and facilitates excretion.
- Intestinal or biliary obstruction may require surgical or endoscopic intervention and removal of the worm.
- In the absence of intestinal perforation or ischemia, conservative management may be attempted first for up to 24 hours.

# Toxocariasis

- Toxocara canis and T. cati infect dogs and cats, respectively; in other hosts, the development of the parasite larvae is arrested.
- Infection occurs worldwide, especially in children.

# Toxocariasis

## Life cycle

- Infection is acquired when soil or food containing eggs is ingested.
- The eggs hatch in the small intestine and release larvae, which penetrate the intestinal wall, enter the portal circulation, and reach the liver and systemic circulation.
- The immature worms bore through the vessel walls and migrate through the tissues, thus leading to secondary inflammatory responses.
- They do not return to the intestinal lumen; therefore, neither eggs nor larvae appear in the feces.
- When larvae become trapped in tissue, they provoke granuloma formation with a predominance of eosinophils. The liver, brain, and eye are the most frequently affected organs.

# Toxocariasis

## Clinical features

- Most infections are asymptomatic. Two major clinical syndromes are recognized:
  1. **Occult infections** are associated with nonspecific symptoms, including abdominal pain, anorexia, fever, and wheezing.
  2. **Visceral larva migrans** is seen most commonly in children with a history of pica. Findings include fever, hepatomegaly, urticaria, and leukocytosis with persistent eosinophilia, hypergammaglobulinemia, and elevated blood group isohemagglutinins. Pulmonary, cardiac, neurologic, and ocular manifestations are often seen.

# Toxocariasis

## Diagnosis

- The diagnosis should be considered in persons with a history of pica, exposure to dogs or cats, and persistent eosinophilia.
- Stool studies are not useful because the larvae do not mature to produce eggs in humans and do not remain in the gastrointestinal tract.
- A definitive diagnosis is made by identification of the larvae in affected tissues, although blind biopsies are low in yield and are not routinely recommended. Ultrasound-guided liver biopsy may be necessary to differentiate visceral larva migrans from hepatic capillariasis.
- A strongly positive ELISA result using excretory-secretory larval antigens provides supportive evidence of infection.

# Toxocariasis

## Treatment

- Albendazole 400 mg twice daily for 5 days or mebendazole 100 to 200 mg twice daily for 5 days is the treatment of choice.
- Significant pulmonary, cardiac, ophthalmologic, or neurologic manifestations may warrant the use of systemic corticosteroids.
- The disease is rarely fatal.

# Hepatic capillariasis

- Capillariasis is a worldwide zoonosis, and infection with Capillaria hepatica is acquired by ingestion of eggs in contaminated soil, food, or water, especially by children under poor hygienic conditions.

## Life cycle

- Larvae released in the cecum penetrate the intestinal mucosa, enter the portal venous circulation, and become lodged in the liver, where adult worms develop within 3 weeks to a size of 20 mm.
- As the female worm dies, it releases eggs into the hepatic parenchyma and produces an intense granulomatous and fibrosing reaction.

# Hepatic capillariasis

## Clinical features

- The features may be similar to those of visceral larva migrans, but it manifests as acute or subacute hepatitis.
- Patients may have tender hepatomegaly and, occasionally, splenomegaly, prominent eosinophilia, mild elevations of serum aminotransferase, alkaline phosphatase, and bilirubin levels, anemia, and an elevated erythrocyte sedimentation rate.

# Hepatic capillariasis

## Diagnosis

- Adult worms or eggs can be detected in liver biopsy or autopsy specimens.
- Associated histologic findings in the liver include necrosis, fibrosis, eosinophilic infiltrate, and granuloma formation.
- Finding of C. hepatica ova in stool likely reflects passage of infected animal material and is not helpful.

## Treatment

- Treatment is generally unsuccessful.
- Mebendazole 200 mg twice daily for 20 days is the drug of choice; alternatively, albendazole 400 mg daily for 10 days may be used.

# Strongyloidiasis

- Strongyloides stercoralis is prevalent in the tropics and subtropics, southern and Eastern Europe, and the United States.
- Infection is usually asymptomatic.

## Life cycle

- Humans are infected by the filariform larvae, which penetrate intact skin, are carried to the lungs, migrate through the alveoli, and are swallowed to reach the intestine, where maturation ensues. Worms are typically found in the duodenum and proximal jejunum.

# Strongyloidiasis

- **Autoinfection** can occur if the rhabditiform larvae transform into infective filariform larvae in the intestine, thus causing persistent infection even decades after exposure.
- **Reinfection** occurs by penetration of the bowel wall or perianal skin and entry into the portal circulation and then the liver.
- Symptomatic infection results from a heavy infectious burden or infection in an immunocompromised person, especially in patients with human T-cell lymphotrophic virus-1, but not in patients with human immunodeficiency virus (HIV) infection.
- A **hyperinfection syndrome** may result from dissemination of filariform larvae into any organ, including the liver, lung, and brain, which is not ordinarily in the life cycle of the nematode.

# Strongyloidiasis

## Clinical features

- As with other helminthic infections, acute infection can lead to a pruritic eruption followed by fever, cough, wheezing, abdominal pain, diarrhea, and eosinophilia.
- When the liver is affected, cholestatic liver biochemical abnormalities can be seen.
- Liver biopsy specimens may show periportal inflammation, and larvae may be observed in intrahepatic bile canaliculi, lymphatic vessels, and small branches of the portal vein.

# Strongyloidiasis

## Diagnosis

- The diagnosis is based on the identification of larvae in the stool or intestinal biopsy specimens.
- Immunodiagnostic tests may be indicated if the organism cannot be demonstrated.
- The presence of an obstructive hepatobiliary picture in a person with established strongyloidiasis suggests possible dissemination.

# Strongyloidiasis

## Treatment

- For acute infection, the drug of choice is ivermectin 200 μg/kg daily for 2 days; alternatively albendazole can be used.
- Retreatment with a second course may be necessary in immunocompromised patients or those with disseminated disease.
- Hyperinfection syndrome requires longer courses of treatment.
- Treatment options are limited following dissemination, and mortality rates are as high as 85%.

# Trichinosis

## Life cycle

- Humans may be infected with Trichinella spiralis by consuming raw or undercooked pork bearing larvae, which are released in the upper gastrointestinal tract, enter the small intestine, penetrate the mucosa, and disseminate through the systemic circulation.
- Larvae can be found in myocardium, CSF, brain, and, less commonly, liver and gallbladder.
- In the small bowel, the larvae develop into adult worms, which release larvae that migrate to striated muscle, where they become encapsulated.

# Trichinosis

## Clinical features

- Clinical manifestations occur when the worm burden is high and include diarrhea, fever, myalgias, periorbital and facial edema, conjunctivitis, and leukocytosis with marked eosinophilia.
- Jaundice may result from biliary obstruction.
- Severe complications include myocarditis, central nervous system involvement, and pneumonitis.

# Trichinosis

## Diagnosis

- This is based on a characteristic history in association with fever and eosinophilia.
- Serologic studies for antibody to Trichinella may not be helpful in the acute phase of infection.
- Muscle biopsy can confirm the diagnosis.
- Rarely, hepatic histologic examination may demonstrate invasion of hepatic sinusoids by larvae.

# Trichinosis

## Treatment

- Corticosteroids are used to relieve allergic symptoms, followed by antihelminthic treatment with albendazole 400 mg twice daily for 8 to 14 days or, alternatively,
- mebendazole 200 to-400 mg three times a day for 3 days, followed by 400 to 500 mg three times a day for 10 days.

# HELMINTHIC INFECTIONS

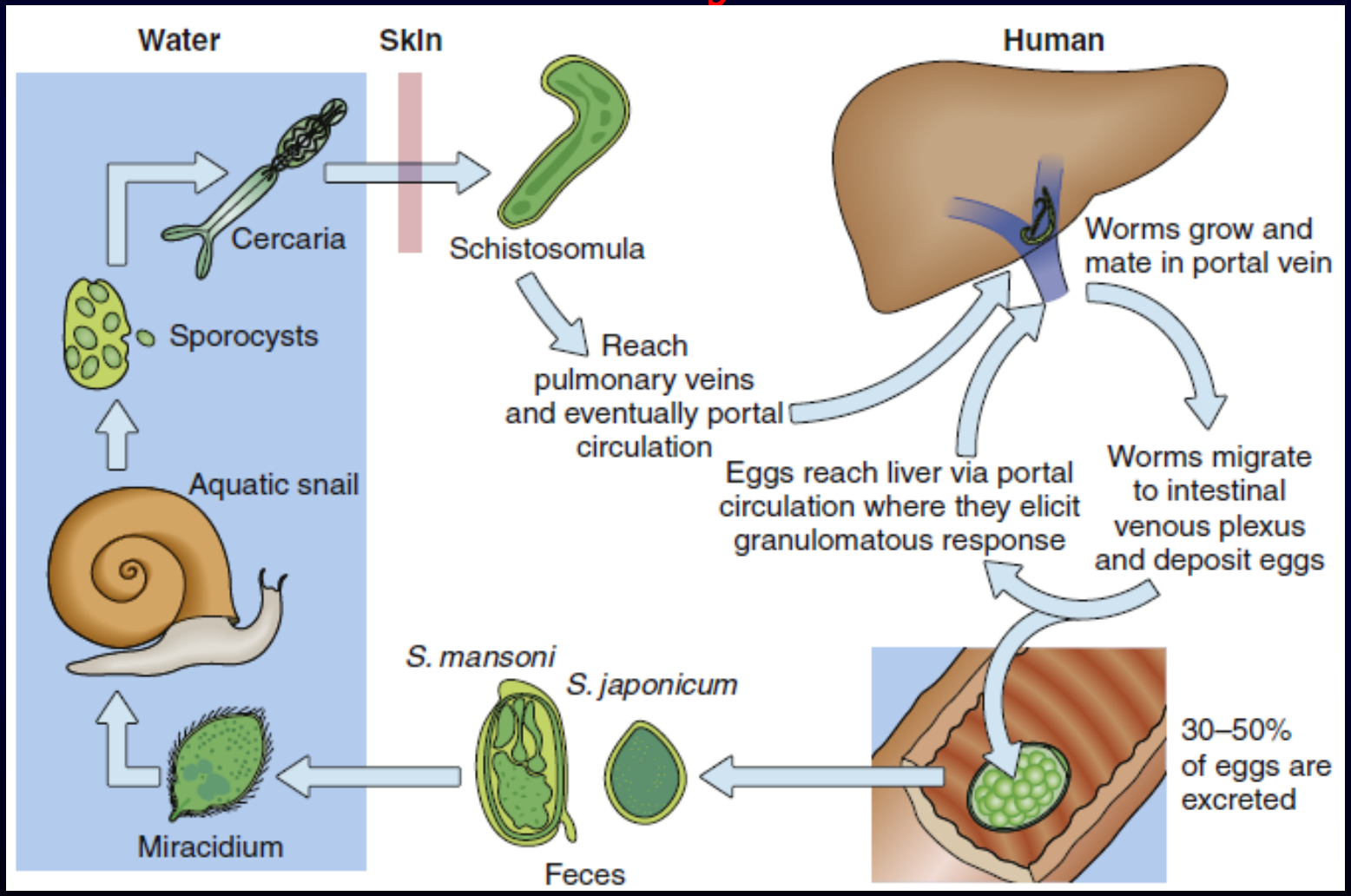
## (TREMATODES )

# Schistosomiasis

- Schistosomiasis (bilharziasis) is caused by trematodes (blood flukes) of the genus Schistosoma.
- Approximately 200 million persons are infected worldwide, with approximately 200,000 deaths annually.
- An estimated 400,000 people, mostly immigrants from endemic areas, are infected in the United States.
- Humans and mammals are the definitive hosts.

# Schistosomiasis

## Life cycle



# Schistosomiasis

## Clinical features

- The severity of clinical symptoms is related to the total worm burden in the host and possibly genetic susceptibility factors and is caused by the host reaction to the schistosomes.
- Acute toxemic schistosomiasis **(Katayama's syndrome)** is believed to result from immune complex formation as a consequence of the host immunologic response to the antigenic challenge by the adult worms and eggs and occurs 4 to 8 weeks after exposure.
- Manifestations include headache, fever, chills, cough, diarrhea, myalgias, arthralgias, tender hepatomegaly, splenomegaly, and eosinophilia.

# Schistosomiasis

- Untreated acute schistosomiasis invariably progresses to chronic disease over many years.
- Mesenteric infection leads to hepatic complications, including periportal fibrosis, presinusoidal occlusion, and, ultimately, presinusoidal portal hypertension, as a result of the inflammatory reaction to eggs deposited in the liver.
- With severe schistosomal infection, portal hypertension becomes progressive, leading to ascites, gastroesophageal varices, and splenomegaly.
- Chronic schistosomal infection may be complicated by increased susceptibility to Salmonella infections.

# Schistosomiasis

- Hepatitis B and C infections are also common in persons living in endemic areas and may accelerate the progression of liver disease and the development of hepatocellular carcinoma.
- Laboratory findings in chronic schistosomiasis include anemia from recurrent gastrointestinal bleeding or hypersplenism, eosinophilia, an elevated erythrocyte sedimentation rate, and increased serum IgE levels.
- Liver biochemical test levels are generally normal until the disease is advanced.

# Schistosomiasis

## Diagnosis

- The diagnosis of acute schistosomiasis should be considered in a patient with an exposure history to fresh water who has abdominal pain, diarrhea, and fever.
- Multiple stool examinations for ova using the Kato-Katz thick smear may be required to confirm the diagnosis, because results are frequently negative in the early phases of disease.
- Serologic testing has proved useful in facilitating earlier diagnosis.
- Sigmoidoscopy or colonoscopy may reveal rectosigmoid or transverse colonic involvement and may be useful in chronic disease when few eggs pass in the feces.
- Ultrasonography and liver biopsy are useful for demonstrating periportal (or “pipestem”) fibrosis but not for diagnosing acute infection.

# Schistosomiasis

## Treatment

- Praziquantel 40 mg/kg given for 1 day in two divided doses is the treatment of choice for infection caused by S. hematobium, S. mansoni, and S. intercalatum; cure rates are 60% to 90%.
- The recommended dose for S. japonicum and S. mekongi is 60 mg/kg divided into 2 or 3 doses.
- Treatment of acute toxemic schistosomiasis requires praziquantel 75 mg/kg for 1 day in three divided doses and, in some cases, prednisone for the prior 2 to 3 days to suppress immune-mediated helminthicidal or drug reactions.
- Periodic treatment of patients in endemic areas will keep the burden of infection low and will minimize chronic complications.

# Schistosomiasis

## Treatment

- Noncirrhotic, presinusoidal portal hypertension may lead to variceal bleeding requiring band ligation or sclerotherapy.
- Advanced chronic schistosomal liver disease can be managed with a distal splenorenal shunt with or without splenopancreatic disconnection or esophagogastric devascularization with splenectomy.
- Since the advent of praziquantel, complicated schistosomal liver disease has become uncommon.

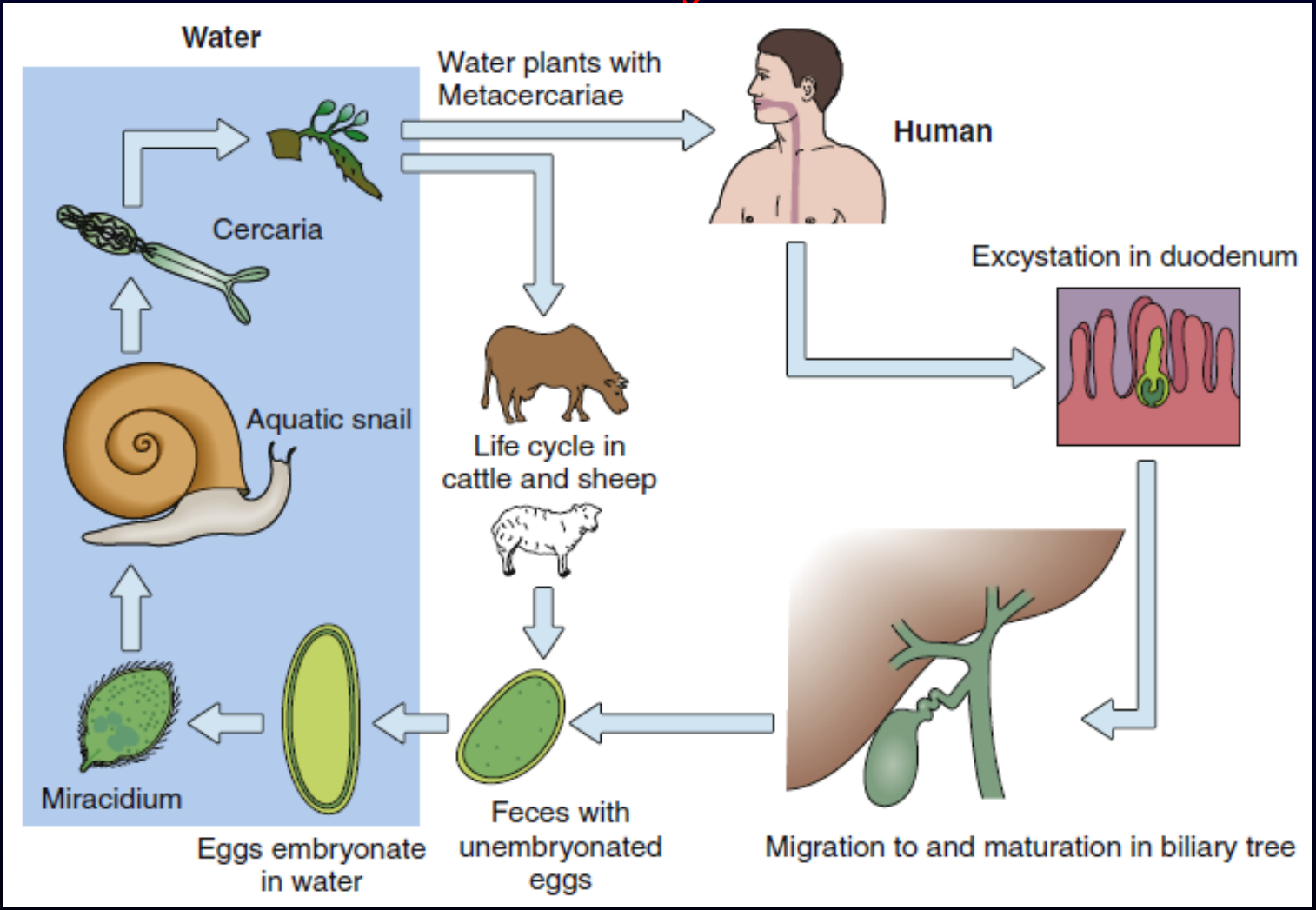
# Fascioliasis

- Fascioliasis, caused by the sheep liver fluke Fasciola hepatica, is endemic in many areas of Europe and Latin America, North Africa, Asia, the Western Pacific, and some parts of the United States, and it causes 2 million infections worldwide.

Parasitic

# Fascioliasis

## Life cycle



# Fascioliasis

## Clinical features

- Fascioliasis is divided into three phases corresponding to three syndromes:
- **Acute**:
  - Migration of young flukes through the liver.
  - This phase is marked by fever, right upper quadrant pain, and eosinophilia. Urticaria with dermatographia and nonspecific gastrointestinal symptoms are common.
  - Physical examination often reveals fever and a tender, enlarged liver. Splenomegaly is reported in up to 25% of cases, but jaundice is rare.
  - Eosinophilia can be profound (occasionally more than 80%).
  - Abnormalities of liver biochemical tests are minimal.

# Fascioliasis

## Clinical features

- **Latent:**
  - Corresponds to the settling of the flukes into the bile ducts and lasts months to years.
  - Affected persons are mostly asymptomatic but may experience vague gastrointestinal symptoms.
  - Eosinophilia persists, and fever can occur.

# Fascioliasis

## Clinical features

- **Chronic obstructive:**
  - Consequence of intrahepatic and extrahepatic bile ductal inflammation and hyperplasia evoked by the presence of adult flukes.
  - This phase may be marked by recurrent biliary pain, cholangitis, cholelithiasis, and biliary obstruction.
  - Blood loss may result from epithelial injury, and rare cases of overt hemobilia have been described.
  - Liver biochemical testing commonly demonstrates a cholestatic pattern.
  - Long-term infection may lead to biliary cirrhosis and secondary sclerosing cholangitis, but no convincing association with malignancies of the liver or biliary tract exists.

# Fascioliasis

## Diagnosis

- This diagnosis should be considered in patients with prolonged fever, abdominal pain, diarrhea, tender hepatomegaly, and eosinophilia.
- Because eggs are not passed during the acute phase, the diagnosis depends on the detection of antibodies to excretory-secretory proteins by EIA.
- In the latent and chronic phases, the diagnosis is made definitively by detection of eggs in stool, duodenal aspirates, or bile.
- Occasionally, ultrasonography or ERCP demonstrates the flukes in the gallbladder and bile duct.

# Fascioliasis

## Diagnosis

- Hepatic histologic findings include necrosis and granuloma formation with eosinophilic infiltrates and Charcot–Leyden crystals.
- Eosinophilic abscesses, epithelial hyperplasia of the bile ducts, and periportal fibrosis may also be seen.

# Fascioliasis

## Treatment

- Unlike other liver fluke infections, praziquantel is not effective for fascioliasis.
- A single dose of triclabendazole 10 mg/kg once or twice is effective; alternatively,
- Bithionol 30 to 50 mg/kg every other day for 10 to 15 doses. or
- Nitazoxanide 500 mg twice daily for 7 days can be used.

# Clonorchiasis

- Clonorchis sinensis, Opisthorchis viverrini, and O. felineus are trematodes (liver flukes) of the family Opisthorchioidea.
- C. sinensis and O. viverrini are widespread in East and Southeast Asia and affect 7 and 1.7 million people, respectively, mostly of lower socioeconomic status.
- O. felineus infects humans and domestic animals in Eastern Europe.
- All three trematodes have similar life cycles and clinical features.

# Clonorchiasis

## Life cycle

- All require two intermediate hosts, an aquatic snail and freshwater fish.
- Eggs are passed in the feces into fresh water, are consumed by snails, and hatch as free-swimming cercariae, which seek and penetrate fish or crayfish and encyst in skin or muscle as metacercariae.
- The mammalian host is infected when it consumes raw or undercooked fish.
- The metacercariae excyst in the small bowel and migrate into the ampulla of Vater and bile ducts, where they mature into 10- to 20-mm adult flukes.
- Infection can be maintained for 2 decades or longer.

# Clonorchiasis

## Clinical features

- Infection is clinically silent or has nonspecific features, with fever, abdominal pain, and diarrhea.
- Chronic manifestations correlate with the fluke burden and are dominated by fever, right upper quadrant pain, tender hepatomegaly, and eosinophilia.
- With a heavy worm burden in the bile ducts, chronic or intermittent biliary obstruction can ensue, with frequent development of cholelithiasis, cholecystitis, jaundice, and, ultimately, recurrent pyogenic cholangitis.

# Clonorchiasis

## Clinical features

- Serum alkaline phosphatase and bilirubin levels are elevated, and mild to moderate elevations of serum aminotransferase levels are also seen.
- Long-standing untreated infection leads to exuberant inflammation resulting in periportal fibrosis, marked biliary epithelial hyperplasia and dysplasia, and a substantially increased risk of cholangiocarcinoma.

# Clonorchiasis

## Clinical features

- **Cholangiocarcinoma** resulting from clonorchiasis or opisthorchiasis tends to be multicentric and arises in the secondary biliary radicles of the hilum of the liver.
- The diagnosis should be suspected in infected persons with weight loss, jaundice, epigastric pain, or an abdominal mass.

# Clonorchiasis

## Diagnosis

- The diagnosis is based on detection of characteristic fluke eggs in the stool.
- Stool examination is usually positive except late in the disease, when biliary obstruction supervenes. In these cases, the diagnosis is made by identifying flukes in the bile ducts or gallbladder at surgery or in bile obtained by postoperative drainage or percutaneous aspiration.
- Endoscopic or intraoperative cholangiography reveals slender, uniform filling defects within intrahepatic ducts that are alternately dilated and strictured and that may mimic sclerosing cholangitis.
- Serologic testing is generally not helpful.

# Clonorchiasis

## Treatment

- All patients with clonorchiasis or opisthorchiasis should be treated with praziquantel, which is uniformly effective in a dose of 75 mg/kg in three divided doses for 2 days.
- Side effects are uncommon and include headache, dizziness, and nausea.
- Alternatively, albendazole 10 mg/kg for 7 days can be used.
- After treatment, dead flukes may be seen in the stool or biliary drainage.
- When the burden of infecting organisms is high, the dead flukes and surrounding debris or stones may cause biliary obstruction necessitating endoscopic or surgical drainage.

# Fungal Liver Disease

# CANDIDIASIS

- Candida species are found worldwide and are common commensal organisms.
- They may cause invasive systemic infection in persons who are severely immunocompromised.
- The liver can become infected by C. albicans in the setting of disseminated, multiorgan disease.
- Conditions that can predispose to disseminated candidiasis include pregnancy, immunologic defects, HIV infection, diabetes mellitus, and severe zinc or iron deficiency.

# CANDIDIASIS

- Most cases of disseminated infections, especially hepatosplenic candidiasis, occur in leukemic patients undergoing high-dose chemotherapy and become manifest during the period of recovery from severe neutropenia.
- In leukemic patients, the frequency is as high as 51% to 91%.
- The disease is often overwhelming, with a high mortality rate.

# CANDIDIASIS

- A less frequent presentation in the compromised host is isolated or focal hepatic candidiasis.
- It is thought to result from colonization of the gastrointestinal tract by Candida, which disseminates locally following the onset of neutropenia and mucosal injury caused by high-dose chemotherapy.
- Resulting fungemia of the portal vein seeds the liver and leads to hepatic microabscesses and macroabscesses.

# CANDIDIASIS

## Clinical features

- In either focal or disseminated candidiasis involving the liver, clinical features include high fever, right upper quadrant abdominal pain and distention, nausea, vomiting, diarrhea, anorexia, and tender hepatomegaly.
- The serum alkaline phosphatase level is nearly invariably elevated, with variable elevations in serum aminotransferase and bilirubin levels.

# CANDIDIASIS

## Diagnosis

- CT of the abdomen is the most sensitive test to detect hepatic or splenic granulomas or abscesses, which are often multicentric.
- In most cases, liver biopsy specimens reveal macroscopic nodules, portal and periportal necrosis with microabscesses, and granulomas surrounding neutrophilic abscesses, as well as characteristic yeast and hyphal forms of Candida.
- Cultures of biopsy material are negative in most cases.
- Polymerase chain reaction testing has been used for diagnosis.
- Laparoscopy may also be employed to confirm the diagnosis.

# Candidiasis.

Contrast-enhanced CT scan of the liver shows multiple hypoattenuating microabscesses less than 1 cm in diameter disseminated throughout the hepatic parenchyma.

# CANDIDIASIS

## Treatment

- If hepatic candidiasis is diagnosed in its focal form, response rates to therapy with intravenous amphotericin B 0.5 to 1.0 mg/kg/day are better (nearly 60%) than in disseminated disease.
- Liposomal amphotericin can be used to reduce the frequency of side effects, especially nephrotoxicity.
- Other options include a combination of amphotericin B with flucytosine, itraconazole, or fluconazole.
- Caspofungin has been shown to be effective in patients with hepatosplenic candidiasis resistant to amphotericin B.
- Occasionally, surgical resection (e.g., splenomegaly in focal disease) may be attempted.
- Despite all efforts, mortality rates remain high.

# HISTOPLASMOSIS

- Infection with Histoplasma capsulatum is acquired through inhalation in an endemic area.
- Most patients are asymptomatic.
- Most symptomatic patients have disease confined to the lungs.
- Severely immunocompromised persons (e.g., with AIDS) in endemic regions are predisposed to disseminated histoplasmosis, affecting mainly those organs rich in macrophages.

# HISTOPLASMOSIS

## Clinical features

- The liver can be invaded in both the acute and chronic forms of progressive disseminated histoplasmosis.
- Fever, weight loss, oropharyngeal ulcers, hepatomegaly, and splenomegaly may be present in chronic disease.
- In children with acute hepatic disease, marked hepatosplenomegaly is universal and is associated with high fever and lymphadenopathy.
- Hepatosplenomegaly is present in 30% of adults with acute disease (often the AIDS-defining illness).
- Serum aminotransferase and alkaline phosphatase levels are often elevated.

# HISTOPLASMOSIS

## Diagnosis

- Yeast forms are small (3 to 4 μm) but can be identified in sections of liver biopsies on standard hematoxylin and eosin staining and are best seen with a Grocott silver stain either diffusely infiltrating the sinusoids or in granulomas.
- The organism is difficult to culture and hardly ever grows from biopsy specimens.
- Serologic testing for complement-fixing antibodies is helpful in confirming the diagnosis.
- In immunocompromised persons, who may not be capable of mounting a significant antibody response, detection of H. capsulatum antigens in urine and serum can be useful.
- The histoplasmin skin test indicates prior sensitization and has no diagnostic value.

# HISTOPLASMOSIS

## Treatment

- Disseminated histoplasmosis should be treated with intravenous amphotericin B.
- Itraconazole is used in mild to moderate infections or to complete therapy after successful response to amphotericin.

# THANK YOU